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# Isolation and Structure Elucidation of the By-Product Formed in the Aminomethylation of α-Methylstyrene[1)]

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Aminomethylation of α-methylstyrene (**1**) leads to 1,2,3,6-tetrahydro-4-phenylpyridine (**3**) as main product, together with a significant amount of a previously unknown by-product. The *N*-methyl, *O*-acetyl-*N*-methyl, *N,O*-diacetyl, *N*-(4-nitrobenzoyl), and (*via* $N \rightarrow O$ acyl-migration) *O*-(4-nitrobenzoyl) derivatives of the by-product were synthesized. By aromatization of the heteroring, 4-phenyl-3-pyridinemethanol (**8a**) was obtained. According to these derivatives and their IR, $^1H$ and $^{13}C$ NMR spectra, the by-product is 1,2,3,6-tetrahydro-4-phenyl-3-pyridinemethanol (**4a**).

**Isolierung und Strukturaufklärung eines bei der Aminomethylierungsreaktion von α-Methylstyrol entstehenden Nebenproduktes[1)]**

Die Aminomethylierung von α-Methylstyrol (**1**) führt zu 1,2,3,6-Tetrahydro-4-phenylpyridin (**3**) als Hauptprodukt, zusammen mit einer beträchtlichen Menge eines bisher unbekannten Nebenproduktes, dessen *N*-Methyl-, *O*-Acetyl-*N*-methyl-, *N,O*-Diacetyl-, *N*-(4-Nitrobenzoyl)- und *O*-(4-Nitrobenzoyl)-Derivate (durch $N \rightarrow O$-Acylwanderung) dargestellt wurden. Die Aromatisierung des Heteroringes lieferte 4-Phenyl-3-pyridinmethanol (**8a**). Gemäß den genannten Derivaten und deren IR-, $^1H$- und $^{13}C$-NMR-Spektren ist das Nebenprodukt 1,2,3,6-Tetrahydro-4-phenyl-3-pyridinmethanol (**4a**).

By aminomethylation of α-methylstyrene (**1**), 1,2,3,6-tetrahydro-4-phenylpyridine (**3**) is obtained through the hydrochloric acid-catalyzed rearrangement of the intermediate oxazine derivative **2**[2-4)].

During attempted reproduction of the published synthesis of compound **3**, in the course of vacuum-distillation of the reaction product a relatively large amount of residue (40 – 50%) was observed; this has not been mentioned by other researchers so far. This substance was isolated as a well-crystallizing base.

The IR spectrum of the base (see Table 1) strongly suggests the presence of a conjugated phenyl ring and of NH and OH groups: a sharp νNH band appears at 3290 $cm^{-1}$ as well as a νOH band between 3200 and 2500 $cm^{-1}$, and the 1060 and 1050 $cm^{-1}$ frequencies of the accompanying νC – O(H) band indicate the presence of a primary hydroxy group. The strong $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands of the phenyl ring, characteristic of monosubstitution, are to be found at 755 and 690 $cm^{-1}$, respectively. A weak νC=C band at 1630 $cm^{-1}$ is due to conjugation between the olefinic C=C bond and the phenyl ring.


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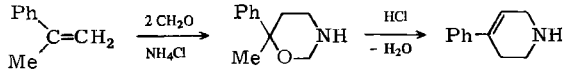
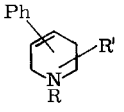
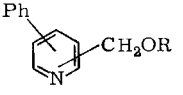


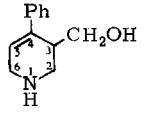
**1** **2** **3**

| | R | R' |
|---|---|---|
| **4** | H | $CH_2OH$ |
| **5** | Me | $CH_2OH$ |
| **6** | Ac | $CH_2OAc$ |
| **7** | Me | $CH_2OAc$ |

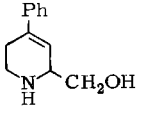




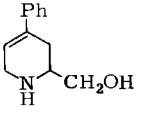
**8**: R = H
**9**: R = Ac



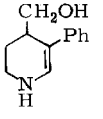
**4a**



**4b**

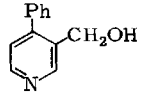


**4c**

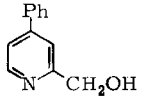


**4d**

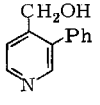
(**5a**-**7a** analogously)



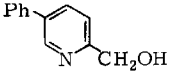
**8a**



**8b**

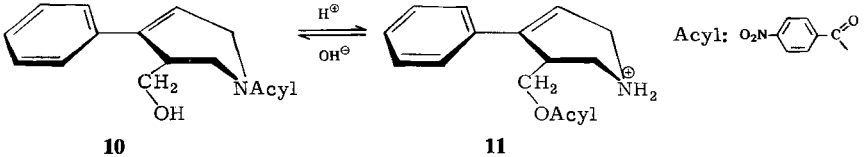


**8c**



**8d**

(**9a** analogously)



**10** **11**

The $^1H$ NMR spectrum (see Table 2) indicates five phenyl and two acidic protons, an olefinic hydrogen, and seven hydrogens adjacent to heteroatoms. All these facts lead to the assumption that by-product **4** is an *N*-non-substituted analogue of the main product **3**, in which a hydroxymethyl substituent is present, too. The four lines of a monosubstituted phenyl ring are to be found in the $^{13}C$ NMR spectrum, together with the carbon signal of the hydroxymethyl group at 64.7 ppm (Table 3), the signals of two olefinic carbons and those of three saturated carbon atoms, again in accordance with structure **4**. The large difference between the chemical shifts of the two olefinic carbons points to the conjugation of the double bond and the phenyl ring (the carbon atoms at the end of a conjugated chain are much more shielded than the "inner" ones[5a]). The relatively low field signals of the three saturated carbon atoms indicate the vicinity of a heteroatom or an unsaturated carbon.

Table 1. IR Data [$cm^{-1}$] of Compounds **4 – 11** in KBr Pellet

| | νNH | νOH[a] | νC=O[b] | νC=C[c] | νC–O | $\gamma C_{Ar}H$[d] | $\gamma C_{Ar}C_{Ar}$[d] |
|---|---|---|---|---|---|---|---|
| **4a**[f] | 3290 | 3300 – 2500 | – | 1630 | 1060[a]<br>1050[a] | 755 | 690 |
| **5a**[f] | – | 3400 – 2500 | – | 1630 | 1045[a] | 770<br>755 | 695 |
| **6a** | | | 1710<br>1635[e] | 1620 | 1235[b]<br>1020[b] | 765<br>760 | 690 |
| **7a**[f] | – | – | 1740 | 1650 | 1240[b]<br>1035[b] | 760 | 700 |
| **8a**[f,g] | – | 3500 – 2500 | – | – | 1025[a] | 755 | 705 |
| **9a**[f,g] | – | – | 1744 | – | 1235[b]<br>1028[b] | 752 | 704 |
| **10**[h] | | 3430 | 1615[e,i] | 1615[i] | 1045[a] | 760 | 708<br>696 |
| **11**[h] | 3320 | – | 1732 | 1610 | 1283[b]<br>1123[b]<br>1105[b] | 770 | 717<br>700 |

[a] Primary hydroxy group. – [b] Ester group. – [c] Group frequency of νC=C character of a conjugated system containing olefinic C=C double bond and an aromatic ring. The relatively high intensity is due to the conjugation. – [d] Characteristic of monosubstituted benzenes. – [e] Amide-I band. – [f] Liquid film. – [g] Strong pyridine bands: 1550, 1450, 890, 650, 640, 620, 580 (**8**), 1593, 1481, 843 (**9**). – [h] $\nu_{as}NO_2$, $\nu_sNO_2$, and $\nu C_{Ar}N(O_2)$ bands: 1522, 1352 and 858 (**10**) and 1524, 1356 and 874 (**11**), respectively. – [i] Overlapping bands.

Table 2. $^1H$ NMR Data of Compounds **4a**, **5a** and **7a – 9a** in $CDCl_3$ ($\delta_{TMS} = 0$, $J$ in Hz in Parentheses)[a]

| | **4a** | **5a** | **7a** | **8a** | **9a** |
|---|---|---|---|---|---|
| 2-H (2H)[b] | 3.02[d]<br>3.35[d] | 2.58[d]<br>3.05[d] | 2.42<br>≈2.8[e] | 8.69 | 8.73 |
| 3-H, m (1H) | 3.45[e] | ≈2.8[e] | 3.08[e] | – | – |
| 5-H (1H) | 6.10<br>t (4) | 6.08<br>dd (3, 2) | 6.00<br>t (3) | 7.12<br>d (5) | 7.22<br>d (5) |
| 6-H (2H)[b] | 3.58[d]<br>3.76[d] | 2.76[d,e]<br>3.37[d] | 2.80[d,e]<br>3.25[d] | 8.35<br>d (5) | 8.50<br>d (5) |
| $CH_2O$ (2H) | 3.7[c]<br>s | 3.80[d]<br>3.60[d] | 4.08<br>d (7) | 4.62<br>s | 5.08<br>s |
| ArH (Phenyl), m (5H) | 7.2 – 7.4 | 7.2 – 7.4 | 7.2 – 7.4 | 7.37[c] | 7.3 – 7.5 |
| $NCH_3$, s (3H) | – | 2.36 | 2.35 | – | – |
| Ac, s (3H) | – | – | 1.92 | – | 2.03 |
| NH, s (1H)[c] | 3.45[e] | – | – | – | – |
| OH, s (1H)[c] | ≈2.7 | ≈5.2 | – | ≈5.8 | – |

[a] The most important $^1H$ NMR data of compounds **6**, **10**, **11** are as follows: $CH_3(OAc)$, s (3H): 2.12 (**6**); $CH_3(NAc)$: 1.94 (**6**); $CH_2O$: 4.95 d (**10**), 4.40 and 4.50 (**11**); 5-H: 6.00 (**10**), 6.15 (**11**); ArH(phenyl): ≈7.33 (**10**), 7.3 – 7.5 (**11**); ArH-2,6($NO_2$phenyl): 7.70 (**10**), 8.10 (**11**); ArH-3,5 ($NO_2$phenyl): 8.35 (**10**, **11**). Because of hindered rotation the signals of *N*-acyl compounds **6** and **10** are partly splitted and broad. In case of **6** at higher temperature the signals coalesce and become sharp. The spectrum of **10** becomes characterless at higher temperatures because of acyl migration (the signals of **10** and **11** are superimposed). – [b] In case of **8** and **9** the intensity is 1H. – [c] Broad singlet. – [d] A or B part (two dd) of an ABX spin system ($\delta A > \delta B$): The values of $J_{AB}$, $J_{AX}$, and $J_{BX}$ in Hz: 13, 2 and 4 (**4**); 11, 1, and 2 (**5**); 11.5, 1, and 4 (7) for 2-H and 12, 2.5, and 4 (**4**); 16, 4, and 1 (**5**); 17, 5, and 2 (**7**) for 6-H and 11, 2.5, and 2 (**5**) for $CH_2O$. – [e] Overlapping signals.

Table 3. $^{13}C$ NMR Data of Compounds **4**–**9** in $CDCl_3$ ($\delta_{TMS} = 0$)

| | **4a**[a] | **5a**[b] | **6a**[c] | **7a**[b] | **8a**[b] | **9a** |
|---|---|---|---|---|---|---|
| C-2 | 45.6 | 55.3 | 41.5(68) | 53.9 | 148.0 | 148.5[d] |
| C-3 | 37.9 | 38.6 | 37.1(12) | 37.2 | 134.3 | 128.0 |
| C-4 | 140.6 | 139.9 | 139.4(11) | 139.7 | 149.3 | 148.5[d] |
| C-5 | 125.6 | 124.4 | 123.7(22) | 125.3 | 124.3 | 123.1 |
| C-6 | 47.7 | 57.9 | 45.6(35) | 55.1 | 150.0 | 150.0 |
| $CH_2$ | 64.7 | 65.8 | 63.8(20) | 65.0 | 60.1 | 60.8 |
| C-1′ | 137.0 | 136.2 | 136.2(45) | 135.1 | 137.9 | 136.9 |
| C-2′,6′ | 126.1 | 126.1 | 126.0 | 125.6 | 128.7 | 127.5[e] |
| C-3′,5′ | 128.5 | 128.4 | 129.2 | 128.4 | 128.5 | 127.5[e] |
| C-4′ | 127.2 | 127.3 | 128.3 | 127.1 | 128.4 | 127.4 |
| $NCH_3$ | – | 45.3 | – | 45.5 | – | – |
| $COCH_3$ | – | – | 21.2<br>21.9(14) | 20.5 | – | 19.3 |
| C=O | – | – | 170.2<br>170.8 | 170.3 | – | 168.8 |

[a] At 63 MHz. – [b] At 25 MHz. – [c] Due to the hindered rotation of the acetamide group the lines of **6** are partly split. The splittings in Hz are given in parentheses. – [d] Overlapping signals, proved by proton-coupled measurement. – [e] Overlapping lines.

The *N*-methyl derivative (**5**) was prepared from compound **4**, and *O*-acetyl derivatives (**6, 7**) were synthesized from **4** and **5**.

The *N*-(4-nitrobenzoyl) derivative (**10**) was prepared, too, and the presence of the two presumed functional groups was supported by reversible $N \rightleftarrows O$ acyl-migration.

To confirm the presence of the tetrahydropyridine ring, **4** was aromatized (**8**) by heating with palladium-carbon in nitrobenzene, and the acetyl derivative (**9**) of the product was also synthesized. Theoretically, the existence of a five- or six-membered alicyclic or pyrroline ring was possible, too. Our assumptions on the structure of **4** were supported by the spectra of derivatives **5**–**9**.

In the IR spectrum of the *N*-methyl derivative (**5**) the νOH and νC–O bands appeared unchanged (Table 1), but there was no νNH band. In the $^1H$ NMR spectrum the *N*-methyl signal was found at 2.36 ppm and, besides the signals of five aromatic, one olefinic and one hydroxy proton, multiplets of further seven, saturated hydrogens could be identified. In the $^{13}C$ NMR spectrum four aromatic, two olefinic, one hydroxymethyl and one of the saturated carbon signals had practically unaltered chemical shifts. The signals of the other two saturated carbons were shifted paramagnetically by approximately 10 ppm. The *N*-methyl carbon signal could be identified at 45.3 ppm. These paramagnetic shifts are consequences of the *N*-substitution the nitrogen being adjacent to two saturated carbons (β-effect[6,7]).

In the IR spectrum of the *N,O*-diacetyl derivative (**6**) the amide-I band is at 1635 $cm^{-1}$, while the ester bands are at 1710 (νC=O), 1235 and 1020 $cm^{-1}$ (νC–O).

In the proton resonance spectrum the acetoxy methyl signal is found at 2.12 ppm, while the signals of the acetamide group (split due to hindered rotation) are observed at 1.90 and 1.98 ppm. Above 100°C, the latter two lines coalesce to a singlet.

In the IR spectrum of the *O*-acetyl derivative of the *N*-methyl compound (7), the ester bands are again present (Table 1), while in the $^1H$ NMR spectrum acetyl and *N*-methyl singlets appear (Table 2). The carbon shifts for 7 are similar to the values for **5**, but the saturated carbons are somewhat more shielded (by 2.8, 1.4, and 1.4 ppm, resp.). Two new lines appear, corresponding to the carbon atoms of the acetyl methyl (20.5 ppm) and carbonyl (170.3 ppm) groups.

The $^1$H NMR spectrum of the aromatized derivative **8** yields unequivocal proof of the assumed structure. Apart from the three singlets with 5H, 2H, and 1H intensity, for the phenyl and hydroxymethyl substituents, only three aromatic H signals could be identified. They have chemical shifts characteristic of pyridine derivatives, with a multiplicity corresponding to two vicinal and one isolated ring proton (two doublets split by 5.2 Hz and a singlet).

Theoretically, six isomers can be assigned to the above spectal data: 3-(hydroxymethyl)-4-phenyl-, 2-(hydroxymethyl)-5-phenyl-, and 2-(hydroxymethyl)-4-phenylpyridine, and the counterparts of these, with the substituents in the opposite positions. However, since the starting compound cannot give rise to an α-phenyl-substituted derivative, only structures **8a – d** need be considered.

This is supported, too, by the β-effect observed for two saturated carbon atoms of methyl compound **5**: in the case of α-phenyl substitution, the *N*-methyl group should have only one saturated neighbouring carbon atom. Structure **8d** may be excluded on the basis of the 5 Hz coupling constant for the *ortho* ring protons, as the $J_{3,4}$ values for pyridines are larger (6.5 – 9.2 Hz[5b]).

Structure **8b** is not likely, partly because the signal of one of the aromatic protons is shifted upfield relative to the other two, making α,γ-substitution improbable, and partly because the *meta*-coupling does not cause significant splitting, which points to the presence of hydrogens in the 2,6-positions. The 2,6-coupling constant is $< 0.6$ Hz. The $J_{3,5}$ coupling constants are of the order of 0 – 2 Hz[5b] and usually yield well observable splitting.

The $^{13}$C NMR spectral data of compound **8**, too, verify the absence of saturated carbons, except for the hydroxymethyl carbon ($\delta$ = 60.1). Besides four phenyl lines, five pyridine carbon signals can be identified. The signals of two unsubstituted carbons (strong) and one substituted carbon (weak) appear close to each other, at low magnetic fields (148.0, 150.0, and 149.3 ppm, respectively), while the two others are shifted upfield and well separated (an intense line at 124.3 and a weak one at 134.3 ppm).

In accordance with the $^1$H NMR data this indicates 3,4-disubstitution of the ring and thus structures **8a** or **c**. For pyridines, $\delta C_\alpha > \delta C_\gamma > \delta C_\beta$ is generally valid[5c] and substitution is mostly accompanied by paramagnetic shift[8]. Hence, the β-position of one of the substituents (supported by the weak, downfield-shifted signal of one of the two more shielded carbons) and the γ-position of the other one is obvious ($C_\gamma$ is more shielded in pyridine by 14 ppm as compared with the α-carbons[5c], and this difference is compensated by the substitution).

Were the substituent in the α-position, the shielding of one of the $C_\alpha$ atoms would decrease relative to the unsubstituted one, while the γ-carbon signal would be situated upfield. Hence, in the direction of low magnetic fields, well-separated lines would appear in a strong-strong-weak sequence, in contrast to the experimental results, which reveal lines very close to each other, the weak one being between the stronger ones.

On this basis, in the correlation of the more probable **8a** and **c**, and the less likely, but not impossible structure **8b** with the unknown **4**, the alternatives **4a – d** are to be considered: the olefinic double bond must be in conjugation with the phenyl ring (besides the reaction pathway and the relatively intense $\nu C=C$ IR band, this is proved by the fact that the $OCH_2$ signal in the spectrum of **7** is a doublet, supporting the presence of an $AcOCH_2CH$ group) and there is only one olefinic proton in the molecule. Thus, structures derived from **8a** and **c**, differing only in the position of the double bond, cannot be considered. At the same time, both **4b** and **c** conform with the above findings and with structure **8b**.

Structures **4b** and **d** may be discounted, as there is no signal at $<2.4$ ppm characteristic of a methylene group $C(sp^3)-CH_2-C(sp^3/sp^2)$ in the proton spectra of compounds **4**–**7**. Thus, a decision must be made between structures **4a** and the corresponding **8a**, and the less probable pair **4c** and **8b**.

Calculation of the $^1H$ NMR shifts of structures **8a** and **b** with the aid of an empirical rule[5d] lends further support to structure **8a** and hence to **4a**. Although the difference between the calculated and measured chemical shifts (Table 4) is only 10% smaller for **8a** than for **8b**, the shift differences for the hydrogens in the various positions are three times larger for the latter. The substituent constants used in the calculation relate to [$D_6$]DMSO solution, while the experimental values were measured in $CDCl_3$ solution. The differences between the measured and calculated shifts therefore include the solvent effect as well. On comparison of the chemical shift differences of hydrogens in various positions in the same molecule, this error is eliminated.

Table 4. Experimentally Measured and Calculated[a] $^1H$ and $^{13}C$ NMR Chemical Shifts and Shift Differences for **8a** and **b**, in ppm units

| Compound | Assignment | Chemical shift observed | Chemical shift calculated | Chemical shift difference H/C[b] | H[c] |
|---|---|---|---|---|---|
| **8a** | δ2-H | 8.69 | 8.82 | −0.13 | |
| | δ5-H | 7.12 | 7.55 | −0.43 | −0.29 |
| | δ6-H | 8.35 | 8.67 | −0.32 | |
| | Δδ(2,5-H) | 1.57 | 1.27 | 0.30 | |
| | Δδ(2,6-H) | 0.34 | 0.15 | 0.19 | 0.20 |
| | Δδ(5,6-H) | 1.23 | 1.12 | 0.11 | |
| **8b**[d] | δ3-H | 8.35 | 7.88 | 0.47 | |
| | δ5-H | 7.12 | 7.53 | −0.41 | 0.32 |
| | δ6-H | 8.69 | 8.77 | −0.08 | |
| | Δδ(3,5-H) | 1.23 | 0.35 | 0.88 | |
| | Δδ(3,6-H) | 0.34 | 0.89 | −0.55 | 0.59 |
| | Δδ(5,6-H) | 1.57 | 1.24 | 0.33 | |
| **8a**[d] | δC-2 | 150.0 | 149.7 | +0.3 | |
| | δC-3 | 134.3 | 136.2 | −1.9 | |
| | δC-4 | 149.3 | 143.7 | +5.6 | 2.5 |
| | δC-5 | 124.4 | 120.3 | +4.1 | |
| | δC-6 | 148.0 | 147.4 | +0.6 | |
| **8b** | δC-2 | 149.3 | 163.7 | −14.4 | |
| | δC-3 | 134.3 | 118.9 | +15.4 | |
| | δC-4 | 148.0 | 144.7 | +3.3 | 8.1 |
| | δC-5 | 124.4 | 117.8 | +6.6 | |
| | δC-6 | 150.0 | 149.4 | +0.6 | |

[a] Using empirical substituent constants (see text). – [b] Difference of the observed and calculated values. – [c] Mean value of the three shift differences. – [d] The "observed" $^{13}C$ NMR chemical shifts of **8b** are the values measured for **8a**, but with a modified assignment, corresponding to the hypothetical structure **8b**. Since we didn't know originally which of the structures **8a** or **8b** is the real one, it was necessary to check which structure fits better with the true chemical shift values.

Similarly to the proton shifts, the much smaller differences between the measured and calculated carbon resonance shifts for **8a** (an average of 2.5 ppm) strongly favour this structure rather than **8b** (average difference 8.1 ppm). As the required substituent constants were not available in the literature, the constants for vinyl and ethyl were substituted instead of those for phenyl and hydroxymethyl, respectively, in the empirical rule[5c].

As final proof, double resonance experiments were conducted with the *N*-methyl compound **5** and its *O*-acetyl derivative **7**: this clarified the dubious assignments of some $^1H$ NMR signals.

However, the double resonance experiments did not give more information concerning the choice between structures **4a** and **c**. DNOE experiments[5e,9] were therefore performed for compound **7**.

On saturation of the aromatic protons, the intensities of the 3-H, the 5-H and, to a lesser extent, the $CH_2O$ signals were enhanced. Upon saturation of the *N*-methyl signal, the intensities of the signals of atoms 2- and 6-H were increased compared to the original spectrum. Thus, structures **4a** and **8a** have been definitely confirmed.

The by-product can be regarded as a 1,3-amino alcohol containing a cyclic nitrogen atom, and for compound **4a** it therefore seemed interesting to investigate the $N \rightarrow O$ and $O \rightarrow N$ acyl-migration characteristic of 1,3-amino alcohols[10-15].

The *N*-benzoyl derivative prepared by Schotten-Baumann acylation was not crystalline, whereas reaction with 4-nitrobenzoyl chloride yielded a well-crystallizing product (**10**). If **10** was heated with hydrochloric acid/ethanol, the hydrochloride of the *O*-acyl derivative (**11**) was obtained. On the action of base, **11** was converted back to the *N*-acyl derivative **10**. These reactions are in conformity with structure **4a** deduced by spectroscopy.

## Experimental Part

Melting points: Boetius (Franz Küstner, Dresden) apparatus, not corrected. – TLC: silica gel G plates, methanol/10% ammonium hydroxide (9:1), detection with iodine vapour. – The compounds were distilled in a Büchi (Flavil, Switzerland) "Kugelrohr" apparatus. – IR spectra: Perkin Elmer 577, KBr pellets and liquid films. – $^1H$ and $^{13}C$ NMR spectra: in $CDCl_3$ solution, 5 mm tubes, room temperature, Bruker WM-250 and a Varian XL-100, 250.13 and 25.14 MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. Complete proton noise decoupling was applied to the $^{13}C$ NMR spectra. Double resonance experiments: conventional CW irradiation of about 0.15 W. – DNOE experiments: Bruker microprogramme 12.5 in the Aspect 2000 pulse programmer. Gated decoupling to generate NOE was used with a delay time of 30 s and a decoupling power of 50 mW. Number of scans 32, relaxation delay 0.1 s, dummy scans 2.

*1,2,3,6-Tetrahydro-4-phenyl-3-pyridinemethanol* (**4a**): 944 g of α-methylstyrene (**1**) was added under stirring and cooling to a mixture of 856 g of ammonium chloride and 3000 ml of 36% formaldehyde solution warmed to 60°C. During stirring, the reaction mixture was cooled to 40°C. 2000 ml of methanol was added and stirring was continued for 20 h at constant temperature. The methanol was distilled off in vacuo, and the residue was mixed with 3000 ml of conc. hydrochloric acid. The mixture was heated to 100°C during stirring, then cooled, made alkaline with 15 N NaOH and extracted with benzene. The benzene phase was dried over potassium carbonate, the benzene was removed, and the residue was distilled in vacuo to give yellow, oily 1,2,3,6-tetrahydro-4-phenylpyridine (**3**) in a yield of 46–50%. B.p. 97–112°C/1 Torr, $n_D^{25} = 1.586$[4].

The distillation residue (approx. 450–500 g) was dissolved in 25% hydrochloric acid and left to stand for a while. The aqueous acid phase was decanted off the resinous tails and evaporated to dryness in the vacuum of a water-jet pump. The residue was dissolved by heating in 2 litres of acetone, and left to crystallize in a refrigerator. The precipitated crystals were filtered off and washed with acetone. After dissolution in water, the solution was made alkaline with ammonium hydroxide and extracted with chloroform. Following drying over potassium carbonate, the

chloroform was evaporated off and the residue was distilled in vacuo. The substance crystallized after the addition of ether. Yield 28 g (ca. 2.5%), b.p. 150°C/4 Torr, m.p. 69–70°C.

$C_{12}H_{15}NO$ (189.3) Calcd. C 76.15 H 7.98 N 7.40 Found C 76.10 H 8.19 N 7.45

*Hydrochloride:* M.p. 228–229°C.

*1,2,3,6-Tetrahydro-1-methyl-4-phenyl-3-pyridinemethanol* (**5a**): 9.46 g (50 mmol) of **4a** was heated for 12 h on a steam-bath with 11.5 g (250 mmol) of formic acid and 10 ml of 36% formaldehyde solution (approx. 0.11 mol). 10 ml of conc. hydrochloric acid was added next and the solution was evaporated to dryness. The residue was dissolved in 25 ml of water and made alkaline with conc. ammonium hydroxide, and the separated oil was extracted with benzene. The extract was dried over potassium carbonate and then evaporated, followed by distillation in vacuo. Yield 9.1 g (89%), b.p. 155°C/4 Torr, m.p. 99–100°C.

$C_{13}H_{17}NO$ (203.3) Calcd. C 76.81 H 6.89 N 8.42 Found C 77.01 H 6.79 N 8.59

*Hydrochloride:* M.p. 183–184°C.

*3-(Acetoxymethyl)-1-acetyl-1,2,3,6-tetrahydro-4-phenylpyridine* (**6a**): 4.73 g (25 mmol) of **4a** was gently boiled for 2 h with 10 g (approx. 0.10 mol) of acetic anhydride in 10 ml of toluene. Afterwards, the solvent, the acetic acid, and the excess acetic anhydride were distilled off in vacuo. When the residue was recrystallized three times from dry ether, a colourless crystalline compound was obtained, 4.5 g (65%), m.p. 70–72°C. TLC showed that the product was homogeneous, but after 1–2 days it deliquesced and had an odour of acetic acid, and a mixture of di- and monoacetate was formed.

$C_{16}H_{19}NO_3$ (273.3) Calcd. C 70.30 H 7.00 N 5.12 Found C 69.90 H 6.71 N 5.20

*3-(Acetoxymethyl)-1,2,3,6-tetrahydro-1-methyl-4-phenylpyridine* (**7a**): To the solution of 10 g (approx. 50 mmol) of **5** in 50 ml of benzene 10 ml (approx. 0.1 mol) of acetic anhydride and a grain of zinc powder were added and the mixture was boiled at 100°C for 12 h. Following evaporation to dryness in vacuo, the residue was dissolved in 20 ml of water, the solution made alkaline with ammonium hydroxide and extracted with benzene. The benzene phase was dried over potassium carbonate. After evaporation of the benzene, the residue was distilled three times in vacuo. The product is a light- and oxygen-sensitive oil. Yield 7.0 g (57%), $n_D^{20}$ = 1.547, b.p. 170°C.

$C_{15}H_{19}NO_2$ (245.3) Calcd. C 73.44 H 7.80 N 5.70 Found C 73.11 H 8.07 N 5.96

*4-Phenyl-3-pyridinemethanol* (**8a**): 9.46 g (50 mmol) of **4a** was stirred with 0.5 g of 10% palladium/charcoal in 43 g (0.35 mol) of nitrobenzene at 135°C for 6 h, the resulting water being removed by bubbling nitrogen through the solution. After cooling, the reaction mixture was poured into an excess of 2 N HCl filtered and then extracted with toluene. The aqueous phase was made alkaline with ammonium hydroxide and the amine was again extracted with toluene. The solution was dried over potassium carbonate, the toluene was removed, and the residue was distilled in vacuo. Yield 7.5 g (81%), b.p. 160°C, m.p. 62–63°C.

$C_{12}H_{11}NO$ (185.3) Calcd. C 77.81 H 5.98 N 7.56 Found C 78.10 H 6.22 N 7.30

*3-(Acetoxymethyl)-4-phenylpyridine* (**9a**): 4.63 g (25 mmol) of **8a** was gently boiled with 5 g (approx. 50 mmol) of acetic anhydride in 10 ml of benzene for 2 h. The solvent, the acetic acid, and the excess acetic anhydride were distilled off in vacuo. The residue was dissolved in ether, the solution washed to neutral with a dilute (5%) solution of sodium hydrogen carbonate, and dried over potassium carbonate. After evaporation of the ether, the residue was distilled in vacuo. Yield 5.0 g (89%), b.p. 160°C/4 Torr, $n_D^{20}$ = 1.5727.

$C_{14}H_{13}NO_2$ (277.3) Calcd. C 73.99 H 5.76 N 6.16 Found C 74.30 H 6.10 N 5.84

*1,2,3,6-Tetrahydro-1-(4-nitrobenzoyl)-4-phenyl-3-pyridinemethanol* (**10**): To the solution of 4.73 g (25 mmol) of **4a** in 50 ml of benzene 50 ml of 1 N NaOH was added, followed by 5.56 g (30 mmol) of 4-nitrobenzoyl chloride in portions during vigorous stirring. The mixture was stirred for 6 h at ambient temperature, the precipitated crystals were then filtered off, and the separated benzene phase was washed to neutral and evaporated to dryness. The residue was united with the filtered crystals and dissolved in benzene. After drying over potassium carbonate and evaporation of solvent, the product was crystallized from benzene. Yield 6.2 g (73%), m.p. 144°C.

$C_{19}H_{18}N_2O_4$ (338.4) Calcd. C 67.44 H 5.36 N 8.27 Found C 67.10 H 5.62 N 8.30

*1,2,3,6-Tetrahydro-3-[(4-nitrobenzoyloxy)methyl]-4-phenylpyridine Hydrochloride* (**11**) *(via N → O acyl migration):* 1.69 g (5.0 mmol) of **10** was dissolved in 50 ml of absol. ethanol, 10 ml of ethanolic (25%) hydrochlorid acid was added, and the reaction mixture was gently boiled. The progress of the reaction was controlled from time to time by TLC. The reaction was completed within 2 h. The mixture was evaporated to dryness, and the residue was filtered and washed with acetone. Yield 1.3 g (69%), colourless crystalline substance, m.p. 195–197°C.

$C_{19}H_{19}ClN_2O_4$ (374.8) Calcd. C 60.72 H 5.09 Cl 9.43 N 7.45
Found C 60.04 H 5.40 Cl 9.61 N 7.72

**10** *via O → N acyl migration:* 0.93 g (25 mmol) of **11** was dissolved in 20 ml of water, 20 ml of benzene was added and under vigorous stirring 2 N NaOH was dropped into the reaction mixture till pH 10. Stirring was continued, and the progress of the reaction was periodically controlled by TLC. The reaction was completed within 1.5 h. The benzene phase was then separated and dried over potassium carbonate. After evaporation of the solvent, a colourless crystalline substance was obtained, 0.45 g (53%). It was recrystallized from benzene, m.p. 142–143°C, no depression of the m.p. with **10** obtained above.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