Bisallyl and Bismethallyl Derivatives of 2,3-Dihydroxypyridine

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2,3-Dihydroxypyridine has been dialkylated with allyl bromide and methallyl chloride to give 1-allyl-3-allyloxy-2-pyridone (**2**) and 1-methallyl-3-methallyloxy-2-pyridone (**3**), respectively. These compounds readily undergo a Claisen rearrangement at 163° to give the bis-1,4-allyl-3-hydroxy-2-pyridone isomers, **4** and **5**, respectively. 2,3-Bisallyloxypyridine (**8**) and 2,3-bismethallyloxypyridine (**9**) were synthesized from 2-chloro-3-hydroxypyridine.

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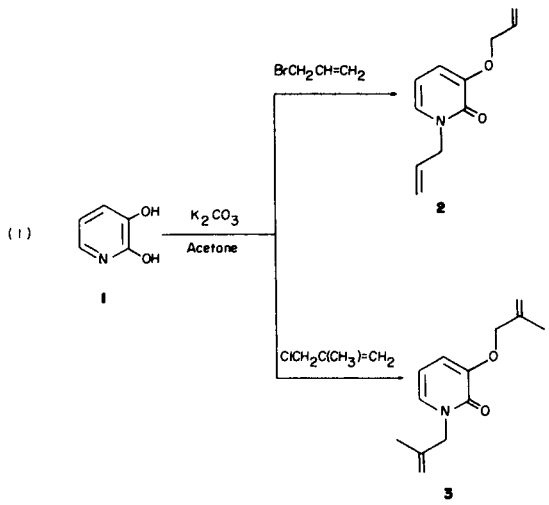
The alkylations of hydroxypyridines are complicated not only by the presence of two nucleophilic sites (N and O) but also by the tautomeric relationship that exists between the 2- and 4-hydroxypyridines and the corresponding pyridones. In the case of 2-hydroxypyridine—2-pyridones, the latter are greatly favored at equilibrium (1). Alkylation of these compounds typically leads to a preponderance of *N*-alkylation, although the ratio of *N*- to *O*-alkylation depends upon the solvent, alkylating agent and the type of base employed in these reactions (2). Alkylation of 3-hydroxypyridines also tends to give *N*-alkylation even in the presence of base (3).

2,3-Dihydroxypyridine (**1**) reacts with methyl iodide to give 3-hydroxy-1-methyl-2-pyridone (4), whereas the dicesium salt of **1** reacts with methyl iodide to give 3-methoxy-1-methyl-2-pyridone (5). Interesting, the dicesium salt of **1** reacts with the polyglycol dibromides to give pyridine-fused crown ethers, the result of 2,3-dialkylations rather than 1,3-dialkylations (5).

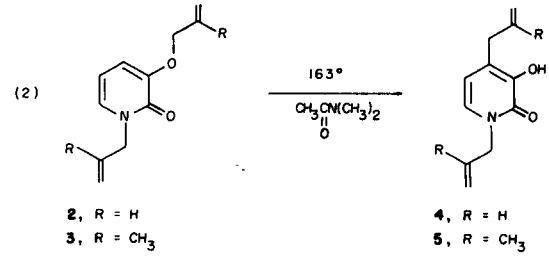
Results and Discussion.

Treatment of 2,3-dihydroxypyridine (**1**) with allyl bromide in acetone in the presence of potassium carbonate gave 1-allyl-3-allyloxy-2-pyridone (**2**) as the major product.



An ^{1}H nmr spectrum of the crude reaction mixture indicated that less than 5% of the 2,3-bisallyloxy isomer, **8** was formed. A similar result was obtained in the reaction of **1** with methallyl chloride to give pyridone **3** as the only isolable product (equation 1). The 1-alkyl-2-pyridones can be distinguished easily from the corresponding 2-alkyloxypyridines by ^{1}H nmr spectroscopy; the C6 proton in the former resonates at *ca.* δ 6.9, whereas this proton appears at *ca.* δ 7.7 in the corresponding pyridines (6).

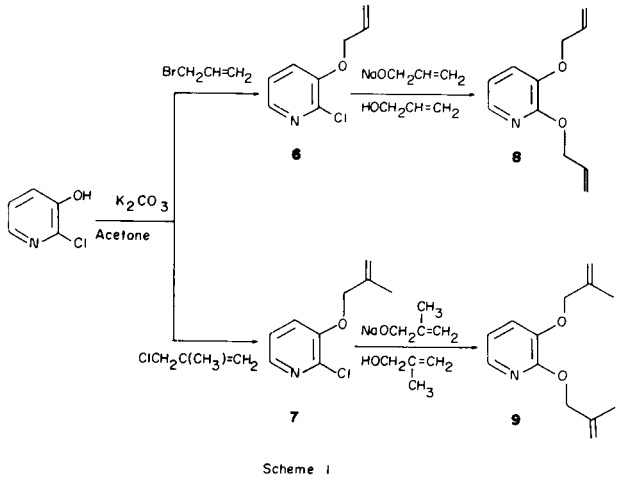
Compounds **2** and **3** readily undergo Claisen rearrangements at 163° to give 1,4-disubstituted pyridones **4** and **5**, respectively (equation 2). The low thermolysis temperature and high yields of these reactions is in contrast with those observed in the Claisen rearrangements of 2-, 3- and 4-allyloxypyridines (reaction temperature of 250°) (6,7), although 2-allyloxypyridine 1-oxide rearranges readily at temperatures below 100° (8).



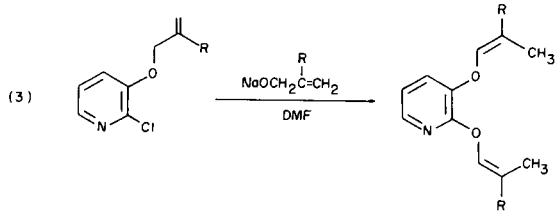
2, R = H
3, R = CH_3
4, R = H
5, R = CH_3

Scheme I outlines the synthesis of the bisallyloxypyridines starting with 2-chloro-3-hydroxypyridine. It is noteworthy that treatment of the chloropyridines **6** and **7** with the sodium allyloxides (9) in dimethylformamide (DMF) rather than in the allylic alcohol solvent, yields as the major product the side chain isomerized propenyl ethers **10** (equation 3). Such isomerizations are known to occur in the presence of strong bases (10).

If reaction (3) is allowed to run to less than 10% completion (5 minutes, 1 *M* base, 50°), the major product is still **10a** (11). It is clear that transferring the sodium allyloxide base from DMF to the alcohol solvent decreases its reactivity; however, not unexpectedly, its basicity is more strongly affected than is its nucleophilicity.



Scheme I



10a, R = H
b, R = CH3

EXPERIMENTAL

General.

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Infrared spectra were determined in potassium bromide or neat on a Perkin-Elmer 281 recording spectrophotometer. The polystyrene absorption at 1601.8 cm^{-1} was used for calibration of the infrared spectra. Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian EM-360 with tetramethylsilane as an internal standard. Microanalyses were carried out by Dr. Franz Kasler of the University of Maryland.

1-Allyl-3-allyloxy-2-pyridone (**2**).

A mixture of 9.8 ml (0.11 mole) of allyl bromide (Baker), 3 g (0.027 mole) of 2,3-dihydroxypyridine (Aldrich), 6.1 g of potassium carbonate and 50 ml acetone was stirred at reflux for 3 days, filtered, and concentrated by rotorary evaporation to give 3.5 g of an oil. The oil (150 mg) was purified by ptlc (0.2 mm silica gel, developed twice with 2:3 ethyl acetate-hexane). The major band, Rf = 0.25, was collected and extracted with 1:4 methanol-methylene chloride to give 130 mg of an oil; ^1H nmr: δ 4.54 (m, 4H), 4.8-5.5 (m, 4H), 5.6-6.3 (m, 2H), 6.02 (dd, J's = 7.0 Hz, 1H), 6.60 (dd, J's = 1.8 and 7.0 Hz, 1H), and 6.86 (dd, J's = 1.8 and 7.0 Hz, 1H); ir (neat): 1652 cm^{-1} (s).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.11; H, 7.01; N, 7.23.

1-Methallyl-3-methallyloxy-2-pyridone (**3**).

A mixture of 16.0 g (0.14 mole) of 2,3-dihydroxypyridine, 50.7 ml (0.53 mole) of methallyl chloride, 250 ml acetone and 32 g of potassium carbonate was stirred at reflux for 3 days. Workup gave an oil which was crystallized from ether-hexane to yield 9.7 g (34%) of **3**; mp 45.5-46.5°; Rf (3:1 ether-petroleum ether) 0.38; ^1H nmr: δ 1.70 (s (b), 3H), 1.80 (s (b), 3H), 4.43 (s (b), 2H), 4.52 (s, (b), 2H), 4.65-5.10 (m, 4H), 5.93 (dd, J's = 7.0 Hz, 1H), 6.55 (dd, J's = 1.8 and 7.0 Hz, 1H) and 6.74 (dd, J's = 1.8 and 7.0 Hz, 1H); ir (potassium bromide): 1645 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.27; H, 8.00; N, 6.40.

3-Hydroxy-1,4-bisallyl-2-pyridone (**4**).

A solution of 900 mg (4.71 mmoles) of crude reaction mixture of **2** in 10 ml of *N,N*-dimethylacetamide was held at reflux for 2 hours. The solution was poured into 50 ml of a mixture of 50-50 ether-petroleum ether and washed with 2 × 50 ml of water. The organic layer was dried (magnesium sulfate) and concentrated by rotorary evaporation to give an oil which was crystallized from ether-hexane to yield 800 mg (89%) of **4**; mp 77-78°; ^1H nmr: δ 3.30 (d (b), J = 6.3 Hz, 2H), 4.55 (d (b), J = 5.5 Hz, 2H), 4.8-5.3 (m, 4H), 5.5-6.1 (m, 2H), 6.03 (d, J = 7.0 Hz, 1H), 6.60 (d, J = 7.0 Hz, 1H), and 7.90 (s (b), 1H); ir (potassium bromide): 3290 (s) cm^{-1} and 1650 (s) cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.26; H, 7.02; N, 7.27.

3-Hydroxy-1,4-bismethallyl-2-pyridone (**5**).

This compound was prepared in the same manner as **4**. The product was crystallized from ether-hexane to yield 1.8 g (90%) of **5**, mp 45-46°; Rf (3:1 ether-petroleum ether) 0.56; ^1H nmr: δ 1.73 (s (b), 6H), 3.23 (s (b), 2H), 4.50 (s (b), 2H), 4.65-5.0 (m, 4H), 6.02 (d, J = 7.2 Hz, 1H), 6.60 (d, J = 7.2 Hz, 1H), and 7.14 (s (b), 1H); ir (potassium bromide): 3220 (s) cm^{-1} and 1645 (s) cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.28; H, 7.79; N, 6.50.

3-Allyloxy-2-chloropyridine (**6**).

A solution of 10 ml (120 mmoles) of allyl bromide, 10 g of 3-hydroxy-2-chloropyridine (Aldrich, 78 mmoles), 20 g potassium carbonate and 170 ml acetone was held at reflux for 84 hours with stirring. The mixture was filtered, concentrated by rotary evaporation, poured into 50 ml of a 20% solution of aqueous sodium hydroxide and extracted with ether. The organic layer was washed once with water, dried (magnesium sulfate) and concentrated by rotary evaporation, distilled, and the fraction which boiled at 67-70° (0.1 mm) was collected, 6.6 g (55%) yield was recovered; ^1H nmr: δ 4.58 (m, 2H), 5.1-5.6 (m, 2H), 5.7-6.4 (m, 1H), 7.15 (m, 2H), and 7.90 (dd, J's = 3.0 Hz, 1H); ir (neat): 1640 cm^{-1} (w), 1560 cm^{-1} (s), and 781 cm^{-1} (s).

Anal. Calcd. for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.91; H, 4.76; N, 8.31.

2,3-Bisallyloxypyridine (**8**).

To a solution of 20 ml of allyl alcohol in which 920 mg (0.04 mole) of sodium had been dissolved was added 3.4 g (0.02 mole) of 3-allyloxy-2-chloropyridine (**6**). This solution was held at reflux for 40 hours, cooled and poured into 100 ml of water. The aqueous mixture was extracted with 2 × 50 ml of ether. The ether extracts were combined and washed with 2 × 50 ml of water and 50 ml of saturated salt solution. The ether layer was dried and concentrated to give a yellow oil which upon distillation gave 2.7 g (64%) yield of a colorless liquid, bp 70-72° at 0.1 mm; ^1H nmr: δ 4.52 (m, 2H), 4.85 (m, 2H), 5.1-5.6 (m, 4H), 5.7-6.5 (m, 2H), 6.69 (dd, 1H, $J_{4,5}$ = 7.7 Hz and $J_{5,6}$ = 4.5 Hz), 7.00 (dd, 1H, $J_{4,5}$ = 7.7 Hz and $J_{4,6}$ = 1.8 Hz) and 7.62 (dd, 1H, $J_{4,6}$ = 1.8 Hz and $J_{5,6}$ = 4.5 Hz); ir (neat): 1640 cm^{-1} (w), 1568 cm^{-1}, 1583 cm^{-1}, 777 cm^{-1}, and 745 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.02; H, 7.00; N, 7.36.

3-Methallyloxy-2-chloropyridine (**7**).

This compound was prepared in the same manner as **6** starting with 5 g (39 mmoles) of 3-hydroxy-2-chloropyridine, 16 ml (0.17 moles) of methallyl chloride, 20 g potassium carbonate in 150 ml acetone. The crude reaction mixture was distilled and 7.0 g (98%) was recovered, bp 80-84° at 0.15 mm; ^1H nmr: δ 1.85 (s (b), 3H), 4.45 (s (b), 2H), 4.8-5.2 (m, 2H), 7.15 (m, 2H) and 7.90 (dd, J's = 3.0 Hz, 1H); ir (neat): 1650 cm^{-1} (w), 1560 cm^{-1} (s), and 781 cm^{-1} (s).

Anal. Calcd. for $C_9H_{10}ClNO$: C, 58.87; H, 5.45; N, 7.63. Found: C, 58.62; H, 5.32; N, 7.59.

2,3-Bismethallyloxypyridine (**9**).

This reaction was carried out in the same fashion as that described for **8** to give 2.9 g (72%) yield of **9**, bp 76-80° at 0.1 mm; ^{1}H nmr: δ 1.85 (s, (b), 6H), 4.40 (s (b), 2H), 4.78 (s (b), 2H), 5.0 (m, 4H), 6.66 (dd, 1H, $J_{4,5}$ = 7.7 Hz and $J_{5,6}$ = 4.5 Hz), 6.96 (dd, 1H, $J_{4,5}$ = 7.7 Hz and $J_{4,6}$ = 1.8 Hz), and 7.62 (dd, 1H, $J_{4,6}$ = 1.8 Hz and $J_{5,6}$ = 4.5 Hz); ir (neat): 1650 cm^{-1} (w), 1670 cm^{-1}, 1688 cm^{-1}, 771 cm^{-1}, and 746 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.23; H, 7.70; N, 6.61.

Reaction of 3-Allyloxy-2-chloropyridine (**6**) with Sodium Alloxide in DMF.

To a solution containing 1.16 g of allyl alcohol and 0.5 g of sodium hydride (as a 50% dispersion in mineral oil--the oil was first removed by washing with pentane) in 10 ml of dry DMF was added 1.7 g (10 mmoles) of **6**. This solution was stirred at 65° for 12 hours, poured into 100 ml of water, and the aqueous mixture was extracted with 2 × 75 ml of ether. The ether portions were combined and washed with 3 × 50 ml of water, dried (magnesium sulfate) and the concentrated to give a yellow oil. Analysis by ^{1}H nmr spectroscopy indicated that *ca.* 65-70% of the product(s) possessed vinyl methyl groups at δ 1.76 and 1.66 (d, J's = 1.8 Hz) in the ^{1}H nmr spectrum. Distillation gave 1.4 g of colorless oil, bp 74-80° (0.15 mm).

When this reaction was repeated for a short time (50°, 5 minutes) an ^{1}H nmr spectrum of the crude reaction mixture indicated that less than 10% reaction had taken place and that the major product was again the enol ether **10a**.

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(11) In the case of the allylic compound, **10a**, the ^{1}H nmr spectrum clearly shows two vinyl methyl doublets (δ 1.66 and δ 1.76, J's = 1.8 Hz). The 1-propenyl groups in **10a** are *cis*-isomers. This assignment is based on literature precedence which has shown that based catalyzed rearrangement of allyl ethers to 1-propenyl ethers gives only the *cis*-isomers (10), and the fact that the ir spectrum of **10a** shows a strong absorption at 1660 cmn^{-1}, a peak characteristic of *cis*-1-propenyl ethers (10).