gen gas was bubbled through for 5 min, during which time the sulfone dropped out of the concentrated solution as clusters of small needles. The reaction mixture was allowed to stand an additional 3–5 min at −10°, then filtered. The filtrate was washed with 10 ml of cold 85% ethanol and dried, giving 838 mg (2.54 mmol, 75% yield) of crystals melting in the range 90–96°, but chromatographically pure and giving an R_f value and UV spectrum identical with those of the material obtained by the first procedure.

Synthesis of 6-(2-Hydroxyethylmercapto)9-β-D-ribofuranosylpurine (4). To a solution of 125 mg (0.38 mmol) of sulfone 1 in 25 ml of water at 25° was added 0.1 ml of mercaptoethanol, and the solution was stirred for 4 hr. The solvent was removed under vacuum and the oil was pumped on for 0.5 hr to remove mercaptoethanol. Absolute ethanol was added and evaporated off, and the oil obtained was dissolved with warming in absolute ethanol and refrigerated. Crystals began to appear after 1 day and were collected after 4 days to give 55 mg (0.168 mmol, 44% yield) of 6-(2-hydroxyethylmercapto)-9-β-D-ribofuranosylpurine (4) as hydroscopic crystals, melting range 105–115°. λ_{max}, nm ($\epsilon \times 10^{-3}$): pH 7, 287 (16.9), 290 (16.9). PMR (DMSO-d_6): δ 8.89 (s, 1 H), 8.86 (s, 1 H), 6.11 (d, J = 5 Hz, 1 H), 5.60 (d, J = 5 Hz, 1 H), 5.00–5.35 (m, 3 H), 4.68 (q, J = 5 Hz, 1 H), 3.92–4.41 (m, 2 H), 3.47–3.84 (m, 6 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.18.

Anal. Calcd for $C_{12}H_{16}N_4SO_5 \cdot \frac{1}{4}H_2O$: C, 43.37; H, 4.97; N, 16.87; S, 9.64. Found: C, 43.33; H, 5.09; N, 16.67; S, 9.44.

Synthesis of 6-Azido-9-β-D-ribofuranosylpurine (6). To 700 mg (2.12 mmol) of sulfone 1 in 100 ml of anhydrous methanol was added 191 mg (2.94 mmol) of sodium azide, and the solution was stirred for 2 hr at 25°, then cooled overnight at 5°. The white amorphous solid was collected and the filtrate reduced in volume and cooled to give more solid material with the correct UV spectrum, a total of 559 mg (1.91 mmol, 90% yield). The product had a UV spectrum identical with that reported for 6-azido-9-β-D-ribofuranosylpurine (6) prepared by another route.[6] Its melting range is 212–214° (lit. 222°). PMR (DMSO-d_6): δ 10.15 (s, 1 H), 8.95 (s, 1 H), 6.18 (d, J = 5 Hz, 1 H), 5.64 (d, J = 6 Hz, 1 H), 5.00–5.37 (m, 2 H), 4.61 (q, J = 5 Hz, 1 H), 3.92–4.40 (m, 2 H), 3.50–3.83 (m, 2 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.25.

Synthesis of *O*-Ethyl 9-β-D-Ribofuranosylpurine-6-thiocarbamate (7). To 763 mg (2.67 mmol) of 6-chloro-9-β-D-ribofuranosylpurine in 30 ml of absolute ethanol was added 895 mg (9.2 mmol) of potassium thiocyanate, and the solution was refluxed 25 hr. The solvent was removed under vacuum and the crude mixture chromatographed on silica gel using an 8–12% linear gradient of methanol in chloroform. The product fractions were collected and the residue after removal of solvents was crystallized from hot ethanol, giving 207 mg (0.52 mmol, 19% yield) of the thiocarbamate, with ¾ ethanols of crystallization, melting range 103–106°. λ_{max}, nm ($\epsilon \times 10^{-3}$): pH 1, 305 (22.8); pH 7, 297 (20.1). PMR after exchange with D_2O and removal of ethanol of crystallization under vacuum): δ 11.94 (s, 1 H), 8.92 (s, 1 H), 8.88 (s, 1 H), 6.13 (d, J = 5 Hz, 1 H), 3.87–4.83 (m, 5 H), 3.53–3.86 (m, 2 H), 1.27 (6, J = 7 Hz, 3 H). TLC, silica gel, 9:1 EtAc–EtOH, R_f 0.32.

Anal. Calcd for $C_{13}H_{17}N_5O_5S \cdot \frac{3}{4}\ CH_3CH_2OH$: C, 44.70; H, 5.51; N, 17.98; S, 8.22. Found: C, 44.70; H, 5.46; N, 18.15; S, 8.24.

Reaction of 6-Methylsulfonyl-9-β-D-ribofuranosylpurine (1) with Thiocyanic Acid Generated in Situ. To a solution of 17.5 mg (0.053 mmol) of sulfone (1) in 20 ml of ethanol were added 0.25 ml of a 1.0 *N* HCl solution and 13 mg (0.135 mmol) of potassium thiocyanate. The mixture was stirred at 25° for 9 hr, at which point a UV spectrum showed only the desired product. Thick layer chromatographic separation (silica gel, 3:1 EtAc–EtOH) gave one main nucleoside product, which was eluted and shown to be *O*-ethyl 9-β-D-ribofuranosylpurine-6-thiocarbamate (7) (0.14 mmol, 27% yield) by its TLC and UV properties.

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Registry No.—1, 53821-41-3; 2, 342-69-8; 4, 53821-42-4; 6, 53821-43-5; 7, 53821-44-6; mercaptoethanol, 60-24-2; 6-chloro-9-β-D-ribofuranosylpurine, 5399-87-1; potassium thiocyanate, 333-20-0.

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Chlorination of 6-Methyl-1,6-naphthyridin-5(6*H*)-one

Ellis V. Brown* and Stanley R. Mitchell

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

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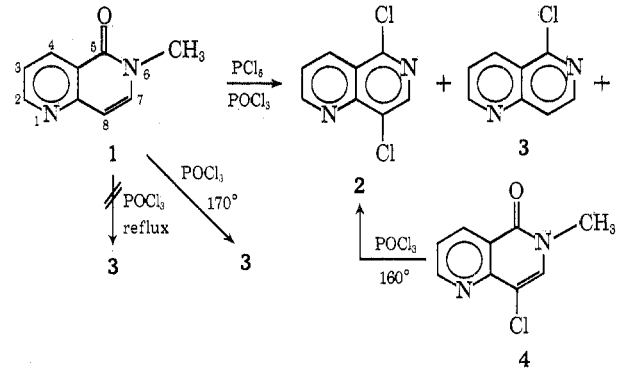
The reaction of 2-methyl-1-isoquinolone using $POCl_3$ and PCl_5 has been reported to yield 1-chloroisoquinoline.[1,2] An investigation by Haworth and Robinson[3] of this reaction found not only the major product but some 1,4-dichloroisoquinoline.

We subjected 6-methyl-1,6-naphthyridin-5(6*H*)-one (1) to the same reaction conditions as above and isolated 5,8-dichloro- (2) and 5-chloro-1,6-naphthyridine (3), 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one (4), and some starting material.



The structure of the major component (2) was established by spectroscopic measurement and chemical derivation. The mass spectrum indicated that the molecule contains two chlorine atoms. It was found by inspection of the nmr spectrum that the 2, 3, and 4 positions did not contain a chloro substituent since its line pattern was similar to that of the starting material and the parent ring compound.[4] The singlet absorption peak at 8.60 was assigned to the 7 proton on the following basis: (a) no cross ring coupling ($J_{4,8}$) was observed, and (b) the chemical shift of analogous protons in the isoquinoline series, 3-H (8.28) of 1,4-dichloroisoquinoline[5] and 4-H (7.80) of 1,3-dichloroisoquinoline.[6]

Since it is known that α and γ halogen substituents in quinoline[7] and isoquinoline[8] undergo nucleophilic displacement, 5,8-dichloro-1,6-naphthyridine was refluxed in a large excess of sodium methoxide in methanol for 4 hr. The mass spectrum of the product showed that the molecule now contains one methoxyl and one chloro group. The nmr spectral line pattern of the 2, 3, and 4 positions was unchanged from the starting material. The singlet proton at

8.10 ppm showed no other coupling (especially $J_{4,8}$). It is concluded from these data that the methoxy and chloro substituents are found in the 5 and 8 positions, respectively.

The second component, 5-chloro-1,6-naphthyridine, was identified by its melting point and nmr[9] and ir spectra.[10]

The third component, 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one, was identified by its ir spectrum and chemical conversion to (2). The spectrum of (4) indicated a carbonyl absorption at 1650, the same wavelength as found in the starting material. When (4) was reacted with $POCl_3$ in a sealed tube at 160°, the product was found to be identical to (2) by mixture melting point and nmr and ir spectra.

Since PCl_5 is a highly active chlorinating agent, reactions were attempted with $POCl_3$ under different conditions. The starting material was quantitatively isolated after a 12-hr reflux period. However, a 62.5% yield of 5-chloro-1,6-naphthyridine was obtained when the reaction took place in a sealed tube at 170° for 20 hr.

In the case of $POCl_3$ at an elevated temperature, only 3 is isolated. However, when a mixture of $POCl_3$ and PCl_5 is used, chlorination at the 8 position also occurs.

Experimental Section

1,6-Naphthyridine-6-methiodide.[4] 1,6-Naphthyridine (4.7 g, 0.036 mol) was dissolved in 40 ml of anhydrous methanol. To this was added 10.03 g (0.0724 mol) of methyl iodide, whereupon the mixture was refluxed 24 hr. The reaction mixture was cooled and 50 ml of ethyl acetate was added. A yellow precipitate was removed by filtration: yield 3.28 g; mp 154–156° (lit.[4] 153–155°). An additional 200 ml of ethyl acetate was added to the filtrate and cooled, and 2.43 g of yellow precipitate was removed: total yield 5.73 g (64%).

6-Methyl-1,6-naphthyridin-5(6*H*)-one.[4] 1,6-Naphthyridine-6-methiodide (5.50 g, 0.0202 mol) was dissolved in 50 ml of water and cooled to 0° in an ice bath. With stirring, 14.2 g (0.0435 mol) of potassium ferricyanide in 50 ml of water and 4.3 g (0.358 mol) of sodium hydroxide in 7.25 ml of water were added simultaneously. The base addition was complete in 10 min and the oxidizing agent addition was complete in 30 min. The solution was stirred at 0° for 90 min, then at room temperature for 27 hr. After continuously extracting the aqueous solution with chloroform for 24 hr, the chloroform was removed *in vacuo*. The residue was sublimed at 90°: yield 2.44 g (75.3%); mp 98–99° (lit.[4] 97–98°).

Chlorination Procedure. To a cold solution of 4.00 g (0.0192 mol) of PCl_5 and 20 ml of $POCl_3$ was added 2.25 g (0.0141 mol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one. The mixture was refluxed with stirring for 24 hr. The excess $POCl_3$ was removed at reduced pressure and ice was added to the residue. After basifying with a saturated solution of sodium carbonate to pH 8, the solution was extracted with chloroform (4 × 50 ml). The chloroform extracts were dried overnight with anhydrous sodium sulfate and the chloroform was removed *in vacuo* at 20°. The residue was placed on an alumina column (Brockman Grade II, 150 g, 2.5 cm diameter) and chromatographed with 5% dichloromethane–carbon tetrachloride (50 ml in 450 ml) until the first band was isolated. Then elution was completed with ethyl acetate.

Fraction A: 5,8-dichloro-1,6-naphthyridine; yield 550 mg (23.9%); mp 113–115°; exact mass ($C_8H_4Cl_2N_2$) 197.969 (calcd 197.975); nmr 9.26 (m, 2-H), 8.67 (m, 4-H), 8.60 (s, 7-H), 7.68 (m, 3-H), $J_{2,4}$ = 1.6 Hz, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 8.8 Hz; ir 2970, 1600, 792, 610 cm^{-1}.

Fraction B: 5-chloro-1,6-naphthyridine; yield 38 mg (2.00%); mp 106–107° (lit.[9] 107°) (after sublimation at 60°).

Fraction C: 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 320 mg (14.3%); mp 199–200° (after sublimation at 155°); exact mass ($C_9H_7ClN_2O$) 194.025 (calcd 194.025); nmr 9.01 (m, 2-H), 8.68 (m, 4-H), 7.52 (s, 7-H), 7.38 (m, 3-H), 3.60 (s, -NCH_3) ($J_{2,3}$ = 4.6 Hz, $J_{2,4}$ = 1.7 Hz, $J_{3,4}$ = 8.0 Hz); ir 3150, 1650, 1570 cm^{-1}.

Fraction D: 6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 400 mg; mp 98–99° (after sublimation at 60°); nmr and ir superimposable with starting material.

5-Methoxy-8-chloro-1,6-naphthyridine. 5,8-Dichloro-1,6-naphthyridine (100 mg, 0.502 mmol, from fraction A) and 200 mg of sodium methoxide were dissolved in 50 ml of anhydrous methanol and heated at reflux for 4 hr. The methanol was evaporated away with a stream of nitrogen and the residue was taken up in 20 ml of a saturated aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (4 × 10 ml) and the extracts were dried overnight with anhydrous sodium sulfate. The chloroform was removed under a stream of nitrogen: yield 85.7 mg (88%); mp 80–82°; exact mass ($C_9H_7ClN_2O$) 194.019 (calcd 194.025); nmr (CCl_4) 8.92 (m, 2-H), 8.32 (m, 4-H), 8.10 (s, 7-H), 7.33 (m, 3-H), 3.98 (s, OCH_3) ($J_{2,3}$ = 4.8 Hz, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 9.4 Hz).

Conversion of 4 into 2. 8-Chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one (4, 256 mg, 1.32 mmol) was combined with 25 ml of $POCl_3$ and heated for 16 hr in a sealed tube at 160°. The excess $POCl_3$ was removed at reduced pressure and the residue was taken up in 20 ml of an ice-cold, saturated, aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (3 × 25 ml) which was dried overnight with anhydrous sodium sulfate. The chloroform was removed and the product was sublimed at 95°: yield 227 mg (88%); mp 112–114°; mp with 2 112–113°.

Phosphorus Oxychloride with 6-Methyl-1,6-naphthyridin-5(6*H*)-one. A. 6-Methyl-1,6-naphthyridin-5(6*H*)-one was heated at reflux with 10 ml of phosphorous oxychloride for 12 hr. The isolation and work-up as described above was used. The starting material was isolated quantitatively and was identical in mp, and ir and nmr spectra.

B. Phosphorus oxychloride (5 ml) and 100 mg (0.625 mmol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one were combined in a sealed tube and heated at 170° for 20 hr. The residue (81.4 mg), isolated as indicated above, was sublimed at 60–70°: yield 64 mg (62.5%); mp 106.5–107° (lit.[9] 107°); ir and nmr spectra were superimposable with that isolated earlier.

Registry No.—1, 19693-54-0; 2, 53731-30-9; 3, 23616-32-2; 4, 53731-31-0; 1,6-naphthyridine-6-methiodide, 37960-58-0; 1,6-naphthyridine, 253-72-5; 5-methoxy-8-chloro-1,6-naphthyridine, 53731-32-1.

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Condensation of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Ethyl Cinnamate and Related Compounds

Chi-Fei Ling, Regina P. Santella, Yvonne H. Shen, and William E. McEwen*

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

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Evidence has been presented[1] that freshly prepared hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds[2]) have the structure 1, but, in solution, an equilibrium mixture of 1, 3, and 4 results. These salts are also presumed to be in equilibrium with the 1,3-dipolar compound 2 (a mesoionic compound) and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds