Synthesis of 3-Hydroxy-6-[^{14}C-methyl]pyrid-2-thione

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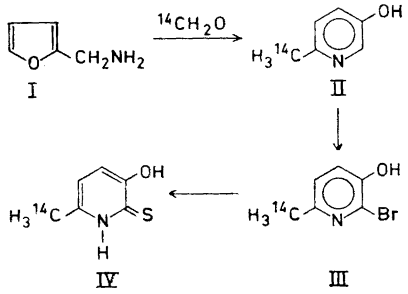
3-Hydroxy-6-methylpyrid-2-thione[1] has shown interesting antimicrobial properties. For closer *in vitro* studies[2] of the inhibition mechanism in *E. coli* a ^{14}C-labelled derivative was required. The simplest way to label the desired molecule appeared to be in the 6-methyl group, especially since the starting material, 3-hydroxy-6-methylpyridine, is available from formaldehyde and furfurylamine[3] and radioactive formaldehyde is commercially available. This would be followed by bromination and thiation as shown below.[1]



The published synthesis of 3-hydroxy-6-methylpyridine had to be modified for small scale work. Equivalent amounts of radioactive formaldehyde and furfurylamine were used to obtain maximum yield of the pyridine based on the radioactive formaldehyde. Excess furfurylamine did not increase the yield. The pyridinol formed in the reaction was best isolated by sublimation from the neutralized, evaporated reaction mixture. Bromination of II was done with bromine in dry pyridine.[1] The sulphur was introduced by heating with KHS in propylene glycol. Excess KHS, a little hydroquinone, and a relatively large volume of solvent in a nitrogen atmosphere were used to prevent oxidation which otherwise becomes important in small scale syntheses of thiolactams under drastic conditions. Despite all precautions, the product obtained was slightly contaminated by the corresponding disulphide. It was best isolated by sublimation.

After each reaction step pure nonradioactive material was added to the reaction mixture for maximum recovery of active material. The pure, isolated material was further diluted by pure material until a convenient amount had been obtained for the next reaction step. The product finally obtained had specific activity 0.91×10^{-2} mC/mmole.

Experimental. TLC on silica gel in the systems BuOH:EtOH:NH_3:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:22:50) were used in this work.

3-Hydroxy-6[^{14}C-methyl]pyridine (II). Furfurylamine (205 mg, 2.16 mmoles) and 37 % formaldehyde (175 mg, 2.16 mmoles) were added to 5 N HCl (1.5 ml) below 0°. Radioactive formaldehyde (2 mg in 0.1 ml of water), specific activity 15 mC/mmole, was then dissolved in this solution. The resultant solution at 0° was added dropwise with stirring over 30 min to 3 N HCl (1 ml) at 105° and the heating continued for another 10 min. The pH was then adjusted to 7.5, 3-hydroxy-6-methylpyridine (25 mg) added, the mixture evaporated and dried *in vacuo* over P_2O_5. The title compound was isolated from this mixture by sublimation at 150°/20 mm Hg; yield 62 mg. Chromatography showed the product to be homogeneous. This was confirmed by radioautography (8 days) on silica gel plates.

2-Bromo-3-hydroxy-6-[^{14}C-methyl]pyridine (III). 3-Hydroxy-6-[^{14}C-methyl]pyridine (62 mg diluted to 100 mg, 0.9 mmole) was dissolved in dry pyridine (2 ml) and bromine (176 mg, 1.1 mmoles) in pyridine (1 ml) added dropwise over 10 min at room temperature, the solution stirred for an hour, evaporated at reduced pressure, the residue triturated with water (3.5 ml) and the solid bromo derivative filtered off. Chromatography showed that some of the bromo compound had been dissolved in the water. Therefore, pure, nonradioactive bromo compound (50 mg) was dissolved in the warm aqueous solution which deposited the bromo derivative on cooling. This material was combined with the first isolated product; total yield 162 mg. The product was chromatographically homogeneous with the same properties as 2-bromo-3-hydroxypyridine perviously prepared[1] and was used in the next step without further purification.

3-Hydroxy-6-[^{14}C-methyl]pyrid-2-thione (IV). Potassium hydrogen sulphide (400 mg, 5.5 mmoles) was dissolved in propylene glycol (20 ml) by heating, the solution allowed to cool to about 160°, 2-bromo-3-hydroxy-6-[^{14}C-methyl]pyridine (162 mg diluted to 300 mg, 1.6 mmoles) and hydroquinone (20 mg) added. The solution was refluxed under dry nitrogen for 20 h, the propylene glycol distilled off at 90° under reduced pressure, the residue dissolved in water (7 ml), the pH of the solution adjusted to about 5 with acetic acid and the solid precipitate collected by filtration. The filtrate was extracted with ethyl acetate, the extracts dried, evaporated and the solid residue combined with the material isolated above. After drying over P_2O_5, the material was sublimed at 190°/20 mm Hg. The yellow solid obtained was recrystallized from benzene; yield 150 mg, m.p. 166–170°. Chromatography showed that the title compound was slightly contaminated by the corresponding disulphide but was otherwise the same as the 3-hydroxy-6-methylpyrid-2-thione previously prepared.[1] Radioautography (5 days) on TLC plates showed the presence of a third component to the extent of less than 2 %.

Activity: 1 μg of the product gives 70 cpm; sp. activity 0.91×10^{-2} mC/mmole.

1. Undheim, K., Nordal, V. and Tjønneland, K. *Acta Chem. Scand.* **23** (1969). *In press.*
2. Laland, S. G. and Bye, G. *Unpublished.*
3. Clauson-Kaas, N. and Meisten, M. *Acta Chem. Scand.* **21** (1967) 1104.

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NMR Studies and Alkaline Hydrolysis of 3-Hydroxy-2-oxo-2-phenyl-3,5,5-trimethyl-1,2-oxaphospholane

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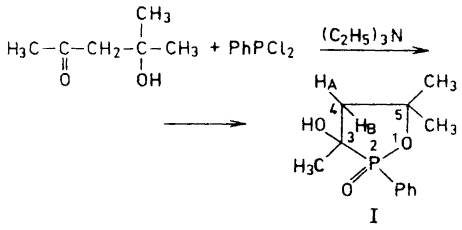
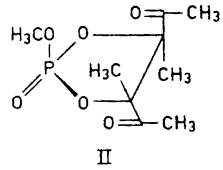
The trivalent phosphorus compounds PCl_6, $PhPCl_2$, and $P(OR)_3$, are known to react with conjugated dienes,[1–5] unsaturated ketones,[6–9] and aliphatic dibromides [10–12] forming derivatives of phospholine, phosphole, oxaphospholine, oxaphospholane, and oxaphosphorinane, respectively. According to this principle of synthesis the 1,2-oxaphospholane I was prepared by the 1,4-addition of dichlorophenylphosphine to diacetone alcohol:



I

The identity of the cyclic compound was established by infrared and proton magnetic resonance spectra, as well as by elementary analysis. The NMR spectrum of the methyl groups in the cyclic compound I consists of four signals (Fig. 1). The signals are found to be solvent dependent, but the separation between two of them remains constant. This is therefore assigned as the phosphorus coupling to the protons of the methyl group in position 3 in I.

It has been observed that the sulfuryl S=O group in cyclic sulfides shows deshielding effect on chemical shifts of protons of ring substituents.[13] Similar effect has also been found for the phosphoryl group as in the racemic cyclic phosphate, 2-methoxy-2-oxy-4,5-diacetyl-1,3,2-dioxaphospholane, II,[14]



II

where the singlet at $\delta = 2.40$ is tentatively assigned to the acetyl group adjacent to the phosphoryl oxygen, while the singlet at $\delta = 2.35$ is assigned to the acetyl group furthest away from this oxygen atom. On the same basis, the singlets at $\delta = 1.57$ and $\delta = 1.47$, are assigned to the CH_3–C groups when methyl is next to, and furthest away from the phosphoryl group, respectively. The methyl groups in position 5 of compound I behaves similarly, the lower signal