Synthesis of ^{32}P- and ^{14}C-Labeled Pesticide, Phoxim

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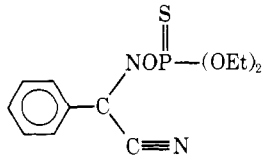
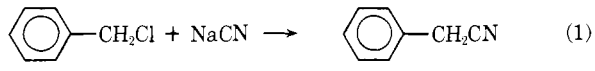
The procedure for synthesizing the pesticide, Phoxim, with ^{32}P in the phosphate portion and ^{14}C in the CN portion is described.

During an investigation of the pesticide, Phoxim, it became necessary to synthesize the parent pesticide with a radioactive P present and to repeat the synthesis with a radioactive C present in the nitrile group.



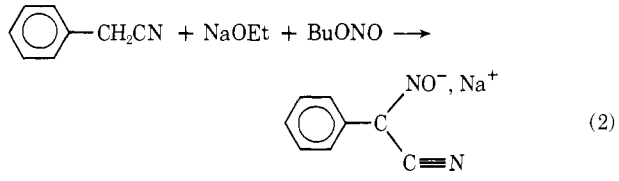
Chemical name, glyoxylonitrile phenyl oxime *O,O*-diethyl phosphorothioate
Trade name, phoxim

Preparation of the Phosphorous-Labeled Compound. The overall reaction was a combination of the work by Vogel (1962), Murray and Williams (1958), Stevens (1963, 1967), and Bayer (1966).



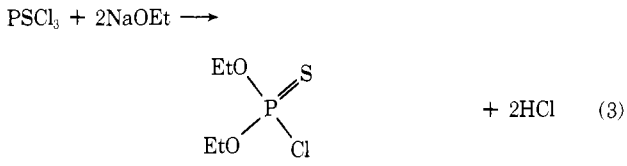
(1)

phenyl acetonitrile



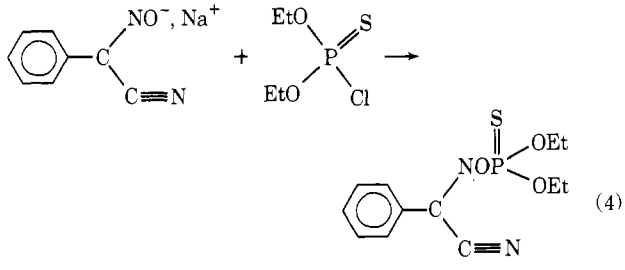
(2)

phenyl glyoxylonitrile oxime, Na salt



(3)

O,O-diethyl phosphorochloridothionate



(4)

phoxim

Before synthesizing any labeled compounds, the reactions were first conducted "cold" on a large scale and then several times on the scales calculated for the labeled product.

Phenyl Acetonitrile. The synthesis of phenyl acetonitrile was conducted using the method outlined by Vogel (1962). One gram of NaCN was weighed into a 10-ml boiling flask and 1 ml of water was then added. The salt was dissolved by heating the flask in a water bath. Benzyl chloride, 2.3 g in 2 ml of 95% ethanol, was added dropwise to the stirred solution. The mixture was heated for 4 hr and cooled, and the NaCl was filtered off. The ethanol was distilled off under reduced pressure and the residue was then dried using molecular sieves. The phenyl acetonitrile was then distilled at 100–105°/10 Torr; yield 1.74 g (73%).

Phenyl Glyoxylonitrile Oxime. Sodium, 2.3 g (0.1 mol), was reacted with 50 ml of absolute ethanol. Phenyl acetonitrile, 11.7 g (0.1 mol), was added dropwise to the cooled sodium ethoxide and then 10.3 g (0.1 mol) of butyl nitrite was added dropwise. The mixture was stirred at room temperature for 1 hr and the volume concentrated to 30 ml by using reduced pressure. Fifty milliliters of ether was added, and the sodium salt of the oxime was filtered off and washed with ether; 8.6 g was recovered, yield 52%. This process gave the pure syn isomer upon initial crystallization. The residue contains a mixture of the syn and anti isomers.

The remaining solvent was removed from the residue and the resulting oil was acidified with HCl. The syn and anti isomers were then separated on a silica gel column using cyclohexane–ethyl acetate (5:1, v/v) as the eluent, the anti isomer eluted first.

Diethyl Phosphorochloridothionate. Sodium, 14.9 g, was added to 300 ml of absolute ethanol. This solution was then slowly added to 53.7 g of $PSCl_3$ in a 500-ml flask. The temperature was kept below 25°. The mixture was poured into 750 ml of water, extracted with 200 ml of methylene chloride, then with 75 ml of methylene chloride, and dried over calcium sulfate. A Rotovac was used to remove the solvent and the product was distilled at 61–69°/5 Torr; 59 g of product was collected, yield 79%.

Phoxim. Diethyl phosphorochloridothionate, 5.7 g, was added dropwise to 6.1 g of sodium phenyl glyoxylonitrile oxime, which was suspended in 20 ml of dry acetone. The mixture was stirred for 1 hr, then poured into water, and extracted with benzene. The solution was dried over molecular sieves, decanted, and then the benzene was removed under reduced pressure. Attempts to purify the product further by distilling at 10^{-3} Torr gave only a small quantity of the desired compound, the *S*-ethyl ester, the oxygen analog, and about 65% residue.

^{32}P-Labeled Phoxim. Two procedures are available, either starting with labeled $PSCl_3$ or, as is now possible, starting with ^{32}P-labeled *O,O*-diethyl phosphorochloridothionate. The best results were obtained with the latter compound.

^{32}P-Labeled diethyl phosphorochloridothionate, 0.16 g (Amersham/Searle, total activity 4 mCi), in 1.4 g of benzene was added to 0.17 g of the sodium salt of phenyl glyoxylonitrile oxime suspended in 1 ml of dry acetone.

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The ampoule which contained the labeled precursor was rinsed with 1 ml of acetone and the washing was added to the reaction mixture. The mixture was stirred for 8 hr, shaken with water, decanted, and dried over molecular sieves. The calculated activity of the compound was 3.6 mCi (2.5 mCi/mmol). The compound was purified by tlc. Silica gel plates were used. The best solvent system was a 20% solution of dimethyl formamide in diethyl ether as a stationary phase and methyl cyclohexane as the mobile phase, R_f 0.24. The chemical purity was in excess of 90% and the radiochemical purity was in excess of 95%.

^{14}C-Labeled Phoxim. The synthesis of the ^{14}C-labeled phoxim involved three reaction steps. First was the preparation of phenyl acetonitrile, then the sodium salt of phenyl glyoxylonitrile oxime was synthesized, and finally phoxim was prepared.

^{14}C-Labeled NaCN (Amersham/Searle, 56.6 mCi/mmol, 1.0 mCi) was added to 0.5 g of unlabeled NaCN. The synthesis of phenyl acetonitrile was conducted in the manner described earlier, with the following changes. Benzyl chloride, 1.1 g in 1 ml of ethanol, was added to the NaCN in 1 ml of water. After being heated and filtered, the solution was dried with molecular sieves and the ethanol was removed under vacuum. The product was not distilled and in the "cold" run no benzyl chloride or benzyl isocyanide was observed in the ir spectrum of the product.

The labeled phenyl acetonitrile was then reacted with 760 mg of butyl nitrite and 4 ml of a sodium ethoxide solution (sodium, 170 mg, was reacted with 40 ml of ethanol, thus forming the solution used in the synthesis). After the reaction was complete, the volume was concentrated to about 2 ml, and then 4 ml of diethyl ether was added to precipitate the sodium salt of the oxime.

The oxime was then reacted with 750 mg of diethyl phosphorochloridothionate. The overall yield for this reaction sequence was 34.2%. The calculated activity for the compound was 0.34 mCi (0.1 mCi/mmol). The chemical and radiochemical purity were the same as with the ^{32}P synthesis.

Structure Identification. Infrared, nmr, and mass spectra of all of the final products were used to prove their composition. These will be presented later when the metabolite investigation is reported.

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Herbicidal Activity of Ester and Amide Derivatives of Substituted Pyrrole-2,4-dicarboxylic Acids

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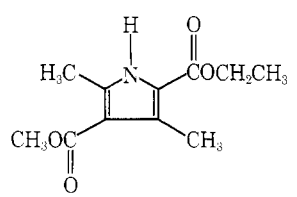
Ester and tertiary amide derivatives of 3,5-dimethylpyrrole-2,4-dicarboxylic acid 4-methyl ester were herbicidally active at low rates. The esters were postemergence herbicides, while the amides showed both preemergence and postemergence activity. Compounds in both series were more active on broadleaved weeds than grasses. The 5-methyl and 4-carbomethoxy substituents and an unsubstituted pyrrole ring nitrogen atom were essential for high activity in these pyrrole herbicides.

Investigations in our laboratories showed that the ethyl ester (1) and ethylmethylamide (2) derivatives of 3,5-dimethylpyrrole-2,4-dicarboxylic acid 4-methyl ester were active as herbicides. Related pyrroles having certain structural features in common with 1 and 2 also had herbicidal activity. In this report the herbicidal activities of compounds 1 and 2 and related pyrroles are presented.



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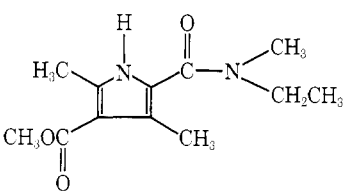

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MATERIALS AND METHODS

Chemical Methods. Diesters of substituted pyrrole-2,4-dicarboxylic acids are readily prepared by nitrosation of a β-keto ester (I) followed by reduction of the resulting oxime II in the presence of a second β-keto ester. The reduction may be effected using zinc dust in acetic acid (Knorr, 1888), sodium amalgam (Knorr and Hess, 1912), or by catalytic hydrogenation (Ochiai *et al.*, 1935). The method of Knorr is convenient in that ester I is converted in acetic acid to the pyrrole without isolation of intermediate II. Using this method compounds **1**, **5**, **6**, **11** (Table II), and **22–39** (Table III) may be prepared.