

AGRICULTURAL FUNGICIDES

V.* PREPARATION OF 3-METHYL-4-(3'-PYRIDYLHYDRAZONO)ISOXAZOL-5-ONE AND RELATED COMPOUNDS

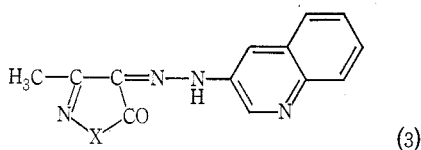
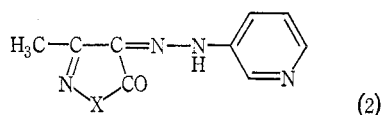
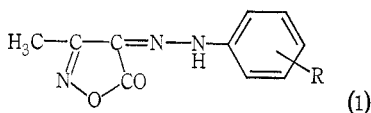
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Abstract

3-Methyl-4-(3'-pyridylhydrazono)isoxazol-5-one, 3-methyl-4-(3'-quinolylhydrazono)isoxazol-5-one, and related pyrazol-5-ones and 1-phenylpyrazol-5-ones have been prepared for examination as fungicides for the control of plant pathogens. They were inactive as foliage fungicides at 1000 p.p.m. against five fungi.

The discovery of the fungitoxic activity of 4-arylhydrazono-3-methylisoxazol-5-ones (1) and the subsequent development of drazoxolon (1; R = 2-Cl) as a fungicide for the control of a number of plant pathogens has stimulated investigations into a possible relationship between chemical structure and biological activity in compounds of this type.¹ In continuation of these investigations we have prepared, and examined as fungicides, isoxazol-5-ones of type (1), where the arylhydrazono group is replaced by 3-pyridylhydrazono and 3-quinolylhydrazono groups, and have extended the study to include corresponding pyrazol-5-ones and 1-phenylpyrazol-5-ones.



By modification of methods adopted for the preparation of 4-arylhydrazono-3-methylisoxazol-5-ones,^{2,3} 3-methyl-4-(3'-pyridylhydrazono)isoxazol-5-one (2; X = O) was obtained as its sparingly soluble sodium salt from the reaction of ethyl acetoacetate and hydroxylamine with diazotized 3-aminopyridine. Careful adjustment

* Part IV, *Aust. J. Chem.*, 1969, **22**, 497.

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¹ Eckhard, I. F., Lehtonen, K., Staub, T., and Summers, L. A., *Aust. J. Chem.*, 1973, **26**, 2705 and references cited therein.

² Schiff, R., *Ber. dt. chem. Ges.*, 1895, **28**, 2731.

³ Summers, L. A., Freeman, P. F. H., and Shields, D. J., *J. chem. Soc.*, 1965, 3312.

of the pH to 6.9–7.1 led to the precipitation of compound (2; X = O). At lower pH values compound (2; X = O) dissolved, presumably due to the formation of its acid salt. By similar means, 3-methyl-4-(3'-quinolyldiazono)isoxazol-5-one (3; X = O) was prepared from 3-aminoquinoline.

The pyrazol-5-one and 1-phenylpyrazol-5-one analogues of (2; X = O) and (3; X = O) have not hitherto been reported although some related pyrazol-5-ones have been studied as dyestuffs and pharmaceuticals.^{4–7} 3-Methyl-4-(3'-pyridylhydrazono)pyrazol-5-one (2; X = NH) was prepared by coupling diazotized 3-aminopyridine with 3-methylpyrazol-5-one and by analogous methods 3-methyl-4-(3'-quinolyldiazono)pyrazol-5-one (3; X = NH) and the 1-phenylpyrazol-5-one derivatives (2; X = NPh) and (3; X = NPh) were obtained. The i.r., u.v., and where possible the n.m.r. spectra of compounds (2; X = O), (3; X = O), (2; X = NH), (2; X = NPh), (3; X = NH), and (3; X = NPh) were examined and were in accord with the assigned structures being comparable with those of the corresponding arylhydrazono compounds.^{3,8,9}

The six compounds, (2; X = O), (3; X = O), (2; X = NH), (2; X = NPh), (3; X = NH) and (3; X = NPh), when tested as protectant foliage fungicides at 1000 p.p.m. against *Alternaria*, *Botrytis*, *Erysiphe*, *Phytophthora*, and *Uromyces* spp., were inactive. The lack of activity shown by (2; X = O) and (3; X = O) compared with the corresponding arylhydrazonoisoxazol-5-ones¹ is presumably due, *inter alia*, to their lower lipid solubility (cf.⁸).

Experimental

Microanalyses were performed by the Australian Microanalytical Service, Melbourne. U.v. absorption measurements were taken with approximately 0.0001M ethanol solutions. N.m.r. spectra (MHz) were determined for 10% w/v solutions in deuteriochloroform using tetramethylsilane as internal standard. I.r. spectra were determined for Nujol mulls or chloroform solutions.

3-Methyl-4-(3'-pyridylhydrazono)isoxazol-5-one (2, X = O)

The method used was a modification of the original procedure of Schiff.² To a mixture of ethyl acetoacetate (0.1 mol), hydroxylamine hydrochloride (0.1 mol), 3-aminopyridine (0.1 mol), concentrated hydrochloric acid (20 ml), and water (50 ml) there was added gradually below 10° a solution of sodium nitrite (8 g) in water (20 ml). The mixture was left overnight. An excess of solid sodium bicarbonate was then added whereupon a yellow-brown precipitate of the sodium salt of 3-methyl-4-(3'-pyridylhydrazono)isoxazol-5-one was obtained. The sodium salt was collected and dissolved in the minimum amount of water at room temperature. The solution was neutralized to pH 6.9–7.1 with dilute hydrochloric acid whereby 3-methyl-4-(3'-pyridylhydrazono)isoxazol-5-one precipitated (yield 40%). It was crystallized from ethanol to afford orange crystals, m.p. 174.5° (Found: C, 53.0; H, 4.1; N, 27.8. C₉H₈N₄O₂ requires C, 52.9; H, 3.9; N, 27.5%). The u.v. spectrum showed λ_{\max} 248 and 385 nm (log ϵ 3.94, 4.31). The i.r. spectrum (Nujol) showed bands at 1730 (CO) and 3240 (NH) cm⁻¹. The n.m.r. spectrum consisted of a singlet at δ 2.33 (CH₃), a multiplet at 7.30–8.80 (aromatic), and a broad singlet at 12.6 p.p.m. (NH).

⁴ Allied Chemical Corp., Neth. Pat. Appl. 6,401,077 (1964) (*Chem. Abstr.*, 1965, **62**, 2853b).

⁵ Willstaedt, H., Borggard, M., and Myrback, K., *Ark. Kemi*, 1949, **1**, 331 (*Chem. Abstr.*, 1950, **44**, 3956c).

⁶ Stright, P. L., Fr. Pat. 1,473,787 (1967) (*Chem. Abstr.*, 1968, **68**, 14064q).

⁷ Back, G., and Fasciati, A., Ger. Pat. 2,039,737 (1971) (*Chem. Abstr.*, 1971, **74**, 127535m).

⁸ Lehtonen, K., and Summers, L. A., *Aust. J. Chem.*, 1970, **23**, 1699.

⁹ Jones, R., Ryan, A. J., Sternhell, S., and Wright, S. E., *Tetrahedron*, 1963, **19**, 1497.

3-Methyl-4-(3'-quinolylhydrazono)isoxazol-5-one (3; $X = O$)

Similarly, using 3-aminoquinoline, *3-methyl-4-(3'-quinolylhydrazono)isoxazol-5-one* was obtained as yellow crystals, m.p. 224° (dec.) (yield 50%), from chloroform-ethanol (Found: C, 61.4; H, 3.9; N, 22.3. $C_{13}H_{10}N_4O_2$ requires C, 61.4; H, 3.9; N, 22.5%). The u.v. spectrum showed λ_{\max} 229, 260, 296, and 400 nm ($\log \epsilon$ 4.21, 3.74, 3.46, 4.22). The i.r. spectrum (Nujol) showed a band at 1720 cm^{-1} (CO) and indications of a band at about 3200 cm^{-1} (NH) (cf.³). It was too insoluble to give a satisfactory n.m.r. spectrum.

3-Methyl-4-(3'-pyridylhydrazono)pyrazol-5-one (2; $X = NH$)

To a solution of 3-methylpyrazol-5-one (8 g) and anhydrous sodium acetate (40 g) in ethanol (370 ml) and water (72 ml) there was added gradually below 10° a diazonium solution prepared from 3-aminopyridine (7.6 g), sodium nitrite (6.4 g), concentrated hydrochloric acid (29 ml), and water (120 ml). A yellow solid precipitated almost at once. The precipitate was collected after 12 hr, and crystallized from ethanol to afford orange-yellow crystals of *3-methyl-4-(3'-pyridylhydrazono)pyrazol-5-one*, m.p. 210° (yield 75%) (Found: C, 53.1; H, 4.4; N, 34.8. $C_9H_9N_5O$ requires C, 53.2; H, 4.4; N, 34.5%). The u.v. spectrum showed λ_{\max} 228, 354, and 382 nm ($\log \epsilon$ 3.85, 4.13, and 4.13). The i.r. spectrum (CHCl_3) showed bands at 1680 (CO), 3240 (hydrazono NH) and 3500 (ring NH) cm^{-1} . It was too insoluble to give a satisfactory n.m.r. spectrum.

3-Methyl-4-(3'-quinolylhydrazono)pyrazol-5-one (3; $X = NH$)

Similarly, using 3-aminoquinoline, *3-methyl-4-(3'-quinolylhydrazono)pyrazol-5-one* was obtained as orange crystals, m.p. 260° (yield 80%), from ethanol (Found: C, 61.6; H, 4.5; N, 27.4. $C_{13}H_{11}N_5O$ requires C, 61.7; H, 4.3; N, 27.7%). The u.v. spectrum showed λ_{\max} 231, 292, 307, 354, and 410 nm ($\log \epsilon$ 4.17, 3.56, 3.48, 3.96, 4.16). The i.r. spectrum (Nujol) showed bands at 1680 (CO), 3240 (hydrazono NH), and 3500 (ring NH) cm^{-1} . It was too insoluble to give a satisfactory n.m.r. spectrum.

3-Methyl-1-phenyl-4-(3'-pyridylhydrazono)pyrazol-5-one (2; $X = NPh$)

By similar means using 3-methyl-1-phenylpyrazol-5-one and 3-aminopyridine, *3-methyl-1-phenyl-4-(3'-pyridylhydrazono)pyrazol-5-one* was obtained as orange crystals, m.p. 131° (yield 80%), from ethanol (Found: C, 64.4; H, 4.7; N, 24.9. $C_{15}H_{13}N_5O$ requires C, 64.5; H, 4.7; N, 25.1%). The u.v. spectrum showed λ_{\max} 249 and 381 nm ($\log \epsilon$ 4.30, 4.39). The i.r. spectrum (Nujol) showed a band at 1670 (CO) and indications of a band at 3240 (NH) cm^{-1} (cf.⁹). The n.m.r. spectrum consisted of a singlet at δ 2.35 (CH_3), a multiplet at 7.20–8.80 (aromatic) and a broad singlet at 13.6 p.p.m. (NH).

3-Methyl-1-phenyl-4-(3'-quinolylhydrazono)pyrazol-5-one (3; $X = NPh$)

Likewise, from 3-methyl-1-phenylpyrazol-5-one and 3-aminoquinoline, *3-methyl-1-phenyl-4-(3'-quinolylhydrazono)pyrazol-5-one* was obtained as red-orange crystals, m.p. 209° (yield 70%), from ethyl acetate (Found: C, 69.0; H, 4.8; N, 21.0. $C_{19}H_{15}N_5O$ requires C, 69.3; H, 4.6; N, 21.3%). The u.v. spectrum showed λ_{\max} 248 and 400 nm ($\log \epsilon$ 4.34, 4.36). The i.r. spectrum (Nujol) showed a band at 1665 (CO) and indications of a band at 3200 (NH) cm^{-1} . It was too insoluble to give a satisfactory n.m.r. spectrum.

Acknowledgments

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