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A DIRECT PREPARATION OF 2-ARYL-4-ETHOXYCARBONYL-3-PYRAZOLIN-5-ONES FROM ARYL HYDRAZINES

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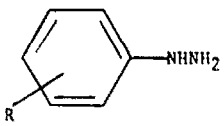
Abstract: Aryl hydrazines (1) possessing an electron-withdrawing substituent on the phenyl ring, on treatment with diethyl (ethoxymethylene)malonate in ethanolic sodium ethoxide solution, have directly afforded 2-aryl-4-ethoxycarbonyl-3-pyrazolin-5-ones (4). Spectroscopic evidence is presented to differentiate these compounds (4) from their 1-aryl isomers (3).

In the course of our work on the preparation of novel N-acyl derivatives of ampicillin,[1] we have synthesised pyrazolinone esters of two general structural types, viz. 1-aryl-4-(ethoxycarbonyl)pyrazolinones (3) and their 2-aryl isomers (4). We herein report a novel direct preparation of certain 2-aryl pyrazolinones (4) from the corresponding free aryl hydrazines (1) and diethyl (ethoxymethylene)malonate (8).

The preparation of 1-aryl pyrazolinone esters (3) from the corresponding hydrazines (1) and diethyl (ethoxymethylene)malonate (8) is well established. For example, Claisen and Haase[2,3] obtained the acyclic product (2a) on treatment of phenylhydrazine (1a) with diethyl (ethoxymethylene)malonate; the diester (2a) was then cyclised to pyrazolinone (3a) on heating to 175°. More conveniently, (3a) has been obtained almost quantitatively from (2a) on heating the latter in refluxing aqueous potassium carbonate solution.[4] The gross structure of pyrazolinone (3a) was established by chemical degradation.[2] More recently, Newman and Pauwells[5,6] have carried out a detailed spectroscopic study of this and other pyrazolin-5-ones. They concluded that 4-ethoxycarbonyl-1-phenylpyrazolin-5-one (3a) can exist in both this NH 3-pyrazolin-5-one form and the tautomeric hydroxypyrazole form (6a). Structural assignments for the compounds prepared during the course of our work are discussed below; meanwhile we will use the 3-pyrazolin-5-one tautomeric forms (3) and (4) to refer to the 1 and 2-aryl heterocyclic isomers respectively.

2-Aryl pyrazolinones (4) are less well documented than their 1-aryl isomers (3). The only preparation known to us of a 2-aryl isomer involves the reaction of phenyl acetyl hydrazide (7) with diethyl (ethoxymethylene)malonate (8) in phosphorus oxychloride[3,7]. The parent 2-phenyl pyrazolinone (4a) is obtained after aqueous work-up. We have repeated this procedure in up to forty percent yield. In this case the amino group α to the phenyl ring of hydrazide (7) is rendered more nucleophilic than the acetylated β-amino group. Presumably the latter function is first converted to an imino phosphoryl group during treatment with phosphorus oxychloride and is subsequently liberated as the protonated nitrogen of the pyrazolinone (4a) on aqueous hydrolysis.

Alternatively we sought a simpler method of preparing a range of 2-aryl pyrazolinones (4), preferably directly from the unmasked parent hydrazines (1)



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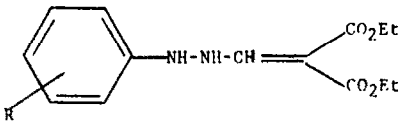

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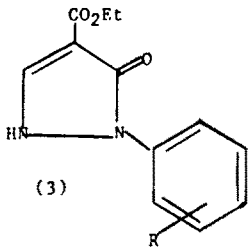

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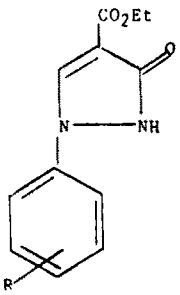

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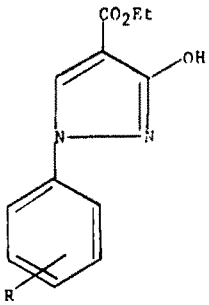

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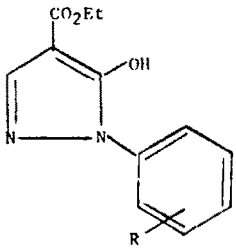

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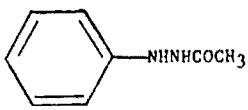

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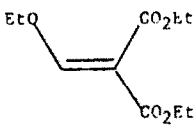

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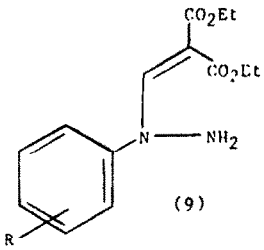

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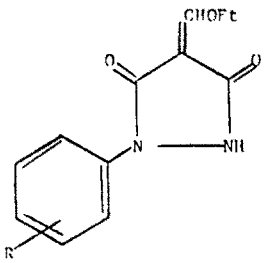

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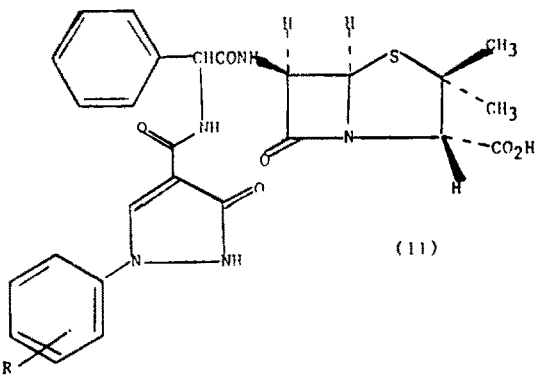

(11)

For all structures:

(a) R = H
(b) R = p-Br
(c) R = m-Br
(d) R = p-SO_2Me
(e) R = m-NO_2
(f) R = p-NO_2

and diethyl (ethoxymethylene)malonate (8). Such a preparation would involve reversing the relative nucleophilicity of the two amino groups normally displayed by 1-aryl hydrazines (1). The β-amino group of phenylhydrazine (1a) and other aryl substituted analogues preferentially reacts with the ethoxymethylene group of malonate (8) under neutral conditions (see above[3,8]). We have also shown that hydrazines (1c, d, e) react in the same way with diethyl (ethoxymethylene)malonate under mildly acidic conditions in refluxing ethanol to give the β-condensation products (2c, d, e). Moreover, we have shown that hydrazines (1a-e) react with malonate (8) and potassium carbonate in refluxing ethanol or water to give directly the 1-aryl pyrazolinones (3a-e). However, we hoped that if we used a sufficiently strong base, the greater acidity of the proton on the nitrogen α to the phenyl ring would render this α-nitrogen the more nucleophilic. Thus we hoped to prepare 2-aryl pyrazolinones (4) via the intermediacy of (9). There is precedent for reversing the relative nucleophilicities of the nitrogens of phenylhydrazine in this way in the work of Ege and Franz.[9]

When ethoxymethylene malonate (8) was added to phenylhydrazine (1a) in either ethanolic sodium ethoxide or tert-butanol containing potassium tert-butoxide, the desired 2-phenyl pyrazolinone (4a) was detectable in the reaction product. At best, however, the isolated yield of (4a) was poor and the acyclic β-condensation product (2a) was also obtained. However, we found that by choosing a suitable electron-withdrawing group on the aryl ring of the hydrazine (1), we could improve the yield of the desired pyrazolinone (4) to [in the case of the m-nitrophenyl pyrazolinone (4e)] almost quantitative. Table 1 shows the yields of 2-aryl pyrazolinones (4b-f) isolated from the reaction of ethoxymethylene malonate (8) with the respective hydrazine (1b-f) in ethanolic sodium ethoxide. Presumably the m-nitro group of hydrazine (1e) assists deprotonation of the amino group α to the aryl ring because of its strong electron-withdrawing effect; however, the anion cannot be stabilised in the manner available to that of the p-nitro isomer (1f), where the charge is presumably so delocalised that the β-amino group remains the more nucleophilic. Thus in this last case, the 1-aryl isomer (3f) was still obtained using ethoxide catalysis.

STRUCTURAL ASSIGNMENTS

1-Aryl Pyrazolinones (3). The parent phenyl (3a) and p-bromophenyl (3b) analogues have already been reported; pyrazolinone (3a) in particular has been extensively studied.[5,6] In addition to being obtained directly from the parent hydrazine, the novel 1-aryl pyrazolinones (3c-e) were prepared from the isolated intermediates (2c-e), which can readily be characterised by their proton n.m.r. spectra as being the β-adducts shown. In each of these compounds the (=CH-NH-) group appears as an AX quartet (J 11 Hz). On D_2O treatment the higher field (CH) doublet slowly collapses to a singlet as the lower field (NH) signal exchanges. As in the reported preparation of analogues (3a) and (3b), cyclisation of (2c-e) to the 1-aryl isomers (3c-3e) is the obvious reaction pathway. The 1-phenyl pyrazolinone (3a) has been assigned[5,6] to exist as this NH tautomer in chlorinated hydrocarbons, and predominantly as the hydroxypyrazole (6a) in a polar solvent (dimethylsulphoxide), mineral oil dispersion and the solid state. Key infra-red bands used to underpin these structural assignments for (3a:6a) were also displayed by our analogues (3b-f:6b-f). Thus the pyrazolinone forms (3a-f) found in chlorinated hydrocarbons exhibited two carbonyl bands, viz. at 1720-1730 cm^{-1} (ester carbonyl; weak due to its

adopting the s-cis configuration to the ring C=C[5]) and at about 1665 cm^{-1} (pyrazolinone carbonyl). In nujol mull, however, only one carbonyl band was observed. In analogues (**6a-c**) this band has a frequency of about 1710 cm^{-1}, and is assigned as the ester carbonyl,[5] while a fairly weak but distinct band at 3150-3170 cm^{-1} is also observed, characterised as a CH stretch arising from the ring -N=CH-C=C component.[6] In analogues (**6d-f**), hydrogen bonding may lower the single carbonyl frequency in nujol mull to the observed value of 1670-80 cm^{-1}, or alternatively the molecules may exist as pyrazolinones with the ester group enolised;[5] structures (**6d-f**) may predominate in dimethylsulphoxide, where all three exhibit a single broad carbonyl frequency at 1700 cm^{-1}.

2-Aryl Pyrazolinones (4). The physical properties of pyrazolinones (**4a-f**) confirm that they are isomeric with pyrazolinones (**3a-f**). Structures of type (**10**) are discounted not only on spectroscopic grounds, but also chemically. Esters of (**4a-f**) have been converted by us via their derivative acids and acid chlorides to penicillins of general structure (**11**) . Spectroscopic comparison of (**4a-f**) with the 1-aryl isomers (**3a-f**) is again complicated by tautomerism, but we have assigned the pyrazolinone tautomeric forms (**4a-f**) as existing in chlorinated hydrocarbons, while the hydroxypyrazole forms (**5a-f**) may predominate in nujol mull and dimethylsulphoxide. Thus the pyrazolinone forms (**4a-f**) found in chlorinated hydrocarbons again exhibited two infra-red carbonyl bands in a manner analogous to the 1-aryl series. The weak band at 1720-1725 cm^{-1} has again been assigned to the ester carbonyl s-cis to the ring C=C, and the strong band at about 1680 cm^{-1} assigned to the ring pyrazolinone carbonyl. The proton n.m.r. spectra of analogues (**4a**) and (**4b**) in deuteriochloroform show that the singlet assigned to the 3-pyrazolinone proton occurs at approximately 0.5 ppm lower field than the corresponding signal of the 1-aryl isomers (**3a**) and (**3b**), indicating deshielding by the adjacent 2-aryl ring in the former series.

In nujol mull, only one infra-red carbonyl band was again observed in the 2-aryl series, indicating tautomerism to the hydroxypyrazole form (**5a-f**). This normally occurred between 1680-1690 cm^{-1}, which may indicate some degree of hydrogen bonding associated with the ester carbonyl to which this frequency is assigned. Typical broad hydrogen bonded hydroxyl stretch absorptions were observed for compounds (**5a-c; e-f**) at 3200-2600 cm^{-1}. A single broad carbonyl frequency for (**5a**) at 1700 cm^{-1} in dimethylsulphoxide may, as in the isomeric series (**6**), indicate that the hydroxypyrazole form again predominates, with the hydrogen bonding lessened compared to the corresponding nujol mull (single carbonyl frequency, 1685 cm^{-1}). The proton n.m.r. spectra of analogues (**5c-f**) in deuteriodimethylsulphoxide show that the singlet assigned to the pyrazole CH proton occurs at approximately 1.0 ppm lower field than the corresponding signal of the isomers (**6c-f**), again indicating deshielding by the adjacent phenyl ring in the former series.

The ultraviolet spectra of all the 2-aryl pyrazolinone series showed that every analogue exhibited a maximum absorption at 30-50 nm longer wavelength than its corresponding 1-aryl isomer.

Finally, because of the discovery that the p-nitrophenyl hydrazine (**1f**) uniquely gave the 1-aryl pyrazolinone (**3f**) on treatment with diethyl (ethoxymethylene)malonate and ethanolic sodium ethoxide, the assignment given to this 1-aryl isomer was underpinned by unambiguous synthesis of the distinct 2-aryl isomer (**4f**), which was prepared by nitration of the parent 2-phenyl pyrazolinone (**4a**).

Table 1

% Yield of 2-Aryl Pyrazolinones (4) from Hydrazines (1) and Ethoxymethylene Malonate (8) in Ethanolic Sodium Ethoxide

Hydrazine	Pyrazolinone	% Yield	
1a	4a	10	[a]
1b	4b	15	
1c	4c	29	
1d	4d	74	
1e	4e	97	
1f	4f	0 (42)[b]	

[a] $KOBu^t/Bu^tOH$ used rather than NaOEt/EtOH

[b] Yield of 1-aryl pyrazolinone isomer (3f) given in brackets.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer 197 spectrometer. Nuclear Magnetic Resonance spectra were recorded on a Varian EM 360 60MHz spectrometer (tetramethylsilane as internal reference). Ultraviolet spectra were recorded on a Perkin Elmer 554 spectrophotometer.

4-Ethoxycarbonyl-2-phenyl-3-pyrazolin-5-one (4a)

Diethyl (ethoxymethylene)malonate (30.6 ml, 132 mmol) was added to 2-acetyl-1-phenylhydrazine (20.0 g, 132 mmol) in phosphorus oxychloride (240 ml) and the mixture stirred at 70°C for 3 hours under nitrogen. The solution was cooled and then carefully poured into water (1 litre) to give a solution which was subsequently cooled to 10°C by the addition of ice. The resultant precipitate was filtered, washed with water and dried under vacuum. Recrystallisation gave the title compound (10.8 g, 36%), m.p. 149° (from aqueous ethanol); i.r. ($CHCl_3$): ν_{max} 1725 (weak), 1680, 1600, 1585, 1505 cm^{-1}; (Nujol): ν_{max} 3200–2600, 3110, 1685, 1605, 1590, 1540, 1510 cm^{-1}; [$(CH_3)_2SO$]: ν_{max} 1700 cm^{-1}; u.v. (EtOH): λ_{max} 281 nm (log ε 4.16); ^1H n.m.r. ($CDCl_3$): δ1.38 (3H, t, CH_3-C, J = 7 Hz), 4.35 (2H, q, CH_2O, J = 7 Hz), 7.45 (5H, m, aryl protons), 8.05 (1H, s, pyrazolinone 3-proton). (Found: C, 61.82; H, 5.39; N, 11.85. Calc. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.14%).

4-Ethoxycarbonyl-1-phenyl-3-pyrazolin-5-one (3a)

To potassium carbonate (1.38 g, 10.0 mmol) and phenylhydrazine (1.08 ml, 10.0 mmol) in water (50 ml) was added diethyl (ethoxymethylene)malonate (2.16 ml, 10.0 mmol) and the mixture stirred at reflux for two hours under nitrogen. The whole was cooled, washed with ethyl acetate and then acidified to pH 2 (5N hydrochloric acid). The resultant precipitate was filtered, washed with water and dried under vacuum. Recrystallisation gave the title compound (2.05 g, 89%), m.p. 113° (from aqueous ethanol) (lit.[4] 113°); i.r. ($CHCl_3$): ν_{max} 1725 (weak), 1665, 1660, 1580, 1500 cm^{-1}; (Nujol): ν_{max} 3170, 3200–2600, 1715, 1620, 1595, 1530, 1500 cm^{-1}; u.v. (EtOH): λ_{max} 229 nm (log ε 4.16); ^1H nmr ($CDCl_3$): δ1.37 (3H, t, CH_3-C, J = 7 Hz), 4.32 (2H, q, $-CH_2O-$, J = 7 Hz), 7.50 (6H, complex, aryl protons and pyrazolinone 3-proton), 9.10 (1H, br.s, NH, exchangeable D_2O).

Direct preparation of 4-ethoxycarbonyl-2-phenyl-3-pyrazolin-5-one (4a) from the parent hydrazine

Phenylhydrazine (0.11 ml, 1.0 mmol) was dissolved in dry t-butanol (10 ml) and treated sequentially with a 0.25M solution of potassium t-butoxide in t-butanol (8.80 ml) and diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol). The mixture was stirred under nitrogen at room temperature for 4.5 hours. The reaction mixture was diluted with water (10 ml) and the pH lowered to 2.5 (5N hydrochloric acid). The contents were concentrated by evaporation and the residue partitioned between water and ethyl acetate. The organic layer was dried (magnesium sulphate) and evaporated to yield an oil (0.21 g). This was partitioned between potassium carbonate solution and ethyl acetate, and the aqueous layer then separated and acidified to pH 2 (5N hydrochloric acid). Ethyl acetate extraction gave after drying (magnesium sulphate), evaporation and recrystallisation (aqueous ethanol) the desired 4-ethoxycarbonyl-2-phenyl-3-pyrazolin-5-one (22 mg, 10%), identical to the material prepared above (mixed m.p. undepressed).

The ethyl acetate layer containing the material insoluble in potassium carbonate was dried (magnesium sulphate), evaporated and the residue chromatographed on silica (hexane:ethyl acetate [4:1]) to give 2-[2,2-bis(ethoxycarbonyl)ethenyl]-1-phenylhydrazine (**2a**) (50 mg, 18%).

2-*p*-Bromophenyl-4-ethoxycarbonyl-3-pyrazolin-5-one (4b)

p-Bromophenylhydrazine (2.24 g, 12.0 mmol) [previously liberated from the hydrochloride] was dissolved in dry ethanol (50 ml) and treated sequentially with an ethanolic solution of 1M sodium ethoxide (26.3 ml, 26.3 mmol) and diethyl (ethoxymethylene)malonate (2.6 ml, 12.0 mmol), and the whole stirred at room temperature under nitrogen for 3 hours. The reaction mixture was concentrated by evaporation and the residue partitioned between water and ethyl acetate. The pH was then lowered to 2.5 (5N hydrochloric acid) and the organic layer shaken, separated, dried (magnesium sulphate) and evaporated to yield an oil (4.47 g). This, on partitioning between aqueous potassium carbonate solution and ethyl acetate, produced a precipitate of the potassium salt of the title product. The precipitate was filtered, suspended in water and the suspension then acidified to pH 2.5 (5N hydrochloric acid). Ethyl acetate extraction of the resultant mixture gave, after drying (magnesium sulphate) and evaporation, the title product (0.43 g). The potassium carbonate layer from above was acidified to pH 2.5 (5N hydrochloric acid) and extracted with ethyl acetate to give, on drying (magnesium sulphate) and evaporation, a further portion of the title product (0.10 g; combined yield, 15%), m.p. 138° (from aqueous ethanol); i.r. (CH_2Cl_2): ν_{max} 1725 (weak), 1685, 1595, 1585, 1520, 1500 cm^{-1}; (Nujol): ν_{max} 3200-2600, 3120, 1690, 1615, 1580, 1550, 1505 cm^{-1}; u.v. (EtOH): λ_{max} 287 nm (log ϵ 4.32); ^1H nmr ($CDCl_3$): δ1.38 (3H, t, CH_3-C-, J = 7 Hz), 4.38 (2H, q, -CH_2-O-, J = 7 Hz), 7.55 (4H, s, aryl protons), 8.10 (1H, s, pyrazolinone 3-proton). (Found: C, 46.29; H, 3.57; N, 8.96; Br, 25.76. Calc. for $C_{12}H_{11}BrN_2O_3$: C, 46.32; H, 3.56; N, 9.01; Br, 25.68%).

1-*p*-Bromophenyl-4-ethoxycarbonyl-3-pyrazolin-5-one (3b)

p-Bromophenylhydrazine (0.84 g, 4.5 mmol) [previously liberated from the hydrochloride] and potassium carbonate (0.62 g, 4.5 mmol) in water (25 ml) were treated with diethyl (ethoxymethylene) malonate (0.95 ml, 4.5 mmol) and the whole stirred under nitrogen at reflux for 2.5 hours. The reaction mixture was cooled, washed with ethyl acetate and then acidified to pH 2.5 (5N hydrochloric acid). Acidification produced a precipitate which was filtered, washed with water and dried in vacuum to give the title compound (0.40 g, 28%), m.p. 153-4° (from methanol) (lit.[8] 154°); i.r. ($CHCl_3$): ν_{max} 1720 (weak), 1660, 1590, 1570 cm^{-1}; (Nujol): ν_{max} 3200-2600, 3160, 1710, 1620, 1585, 1550, 1510 cm^{-1}; u.v. (EtOH): λ_{max} 250 nm (log ϵ 4.48); ^1H nmr ($CDCl_3$); δ1.41 (3H, t, CH_3C-, J = 7 Hz), 4.38 (2H, q, -CH_2O-, J = 7 Hz), 7.52 (4H, complex, aryl protons), 7.63 (1H, s, pyrazolinone 3-proton), 9.37 (1H, br.s, NH, exchangeable D_2O).

2-m-Bromophenyl-4-ethoxycarbonyl-3-pyrazolin-5-one (4c)

m-Bromophenylhydrazine hydrochloride (0.22 g, 1.0 mmol) in a 0.35M solution of sodium ethoxide in ethanol (8 ml) was treated at room temperature with diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol) in ethanol (2 ml), and the mixture stirred for 1 hour. The solution was then acidified to pH 2.3 with 5N hydrochloric acid and concentrated by evaporation. The resulting solid was filtered, washed with water and hexane, and dried to give a residue which was partitioned between ethyl acetate and saturated aqueous potassium carbonate solution. The aqueous layer was separated, acidified to pH 2.5 (5N hydrochloric acid) and extracted with ethyl acetate. Drying (sodium sulphate) and evaporation gave the title product (0.09 g, 29%), m.p. 156° (from methanol); i.r. (CH_2Cl_2): ν_{max} 3370, 1720 (weak), 1680, 1590, 1580, 1510 cm^{-1}; (Nujol): ν_{max} 3200-2600, 3120, 1690, 1600, 1590, 1540 cm^{-1}; u.v. (EtOH): λ_{max} 285 nm (log ϵ 4.25); ^1H nmr [$(CD_3)_2SO$]: δ1.27 (3H, t, $-CH_3$, J = 7 Hz), 4.20 (2H, q, $-CH_2O-$, J = 7 Hz), 7.45 (2H, complex, aryl protons), 7.82 (1H, d of t, 4-phenyl proton, J = 8, 2 Hz), 8.05 (1H, m, 2-phenyl proton), 8.85 (1H, s, pyrazolinone 3-proton). (Found: C, 46.36; H, 3.58; N, 8.89. Calc. for $C_{12}H_{11}BrN_2O_3$: C, 46.32; H, 3.56; N, 9.01%).

1-m-Bromophenyl-4-ethoxycarbonyl-3-pyrazolin-5-one (3c) (direct preparation)

m-Bromophenylhydrazine hydrochloride (0.22 g, 1.0 mmol) and potassium carbonate (0.28 g, 2.0 mmol) were suspended in dry ethanol (10 ml) and treated with diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol), and the mixture then stirred at reflux under nitrogen for 3 hours. The mixture was cooled, concentrated by evaporation and the residue suspended in water. The pH was lowered to 2.5 (5N hydrochloric acid) and the aqueous layer extracted with ethyl acetate to give, after drying (magnesium sulphate) and evaporation, the title product (0.25 g, 79%), m.p. 133° (from ethanol); i.r. ($CHCl_3$): ν_{max} 1720 (weak), 1660, 1590, 1575 cm^{-1}; (Nujol): ν_{max} 3150, 3100-2600, 1705, 1605, 1575, 1550, 1510 cm^{-1}; u.v. (EtOH): λ_{max} 245 nm (log ϵ 4.35); ^1H nmr ($CDCl_3$): δ1.38 (3H,t, CH_3-C-, J = 7 Hz), 4.30 (2H, q, $-CH_2O$, J = 7 Hz), 7.64 (5H, complex, aryl protons and pyrazolinone 3-proton), 8.7 (1H, br.s, -NH-, exchangeable D_2O); [$(CD_3)_2SO$]: δ1.30 (3H, t, CH_3-C-, J = 7 Hz), 4.21 (2H, q, $-CH_2O-$, J = 7 Hz), 6.5 (1H, br, -OH [pyrazole form]), 7.47 (4H, complex, aryl protons), 7.77 (1H, s, pyrazolinone 3-proton). (Found: C, 46.57; H, 3.61; N, 8.86; Br, 25.51. Calc. for $C_{12}H_{11}BrN_2O_3$: C, 46.32; H, 3.56; N, 9.01; Br 25.68%).

1-m-Bromophenyl-4-ethoxycarbonyl-3-pyrazolin-5-one (3c) (Preparation via isolation of intermediate 2-[2,2-bis(ethoxycarbonyl)ethenyl]-1-m-bromophenylhydrazine (2c))

m-Bromophenylhydrazine hydrochloride (0.22 g, 1.0 mmol) was suspended in dry ethanol (10 ml) and treated with diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol) and the mixture stirred at reflux for 2.5 hours. The reaction mixture was cooled, concentrated by evaporation and the residue partitioned between potassium carbonate solution and ethyl acetate. The organic layer was separated, dried (magnesium sulphate) and evaporated to give a mixture (0.27 g) from which the intermediate (2c) was isolated after chromatography on silica [hexane:ethyl acetate (4:1)] and recrystallisation (0.10 g, 31%), m.p. 105-6° (from chloroform:hexane); i.r. ($CHCl_3$): ν_{max} 1690, 1650, 1600 cm^{-1}; u.v. (EtOH): λ_{max} 279 nm (log ϵ 4.33); ^1H nmr ($CDCl_3$): 1.27, 1.34 (2 x 3H, 2t, $(CH_3-C-)_2$, J = 7, 7 Hz), 4.10, 4.20 (2 x 2H, 2q, $(-CH_2O)_2$, J = 7, 7 Hz), 6.92 (4H, complex, aryl protons), 8.04 (1H, d, C=CH-N, J = 11 Hz, collapses to s with CD_3OD), 9.75 (1H, d, C=C-NH, J = 11 Hz, exchanges with CD_3OD). (Found: C, 47.20; H, 4.93; N, 7.81. Calc. for $C_{14}H_{17}BrN_2O_4$: C, 47.07; H, 4.80; N, 7.84%).

2-[2,2-Bis(ethoxycarbonyl)ethenyl]-1-m-bromophenylhydrazine (2c) (45 mg, 0.126 mmol) was dissolved in dry ethanol (2 ml) and treated with potassium carbonate (18 mg, 0.126 mmol), and the mixture stirred under nitrogen at reflux for 0.75 hours. The mixture was then cooled, diluted with water and acidified to pH 2.5 (5N hydrochloric acid). Ethyl acetate extraction gave after drying (magnesium sulphate) and evaporation the title product (39 mg, 99% from intermediate (2c)), identical to the material prepared directly from m-bromo-phenylhydrazine.

4-Ethoxycarbonyl-2-p-(methylsulphonyl)phenyl-3-pyrazolin-5-one (4d)

p-(Methylsulphonyl)phenylhydrazine (0.37 g, 2.0 mmol) in a 0.25M solution of sodium ethoxide in ethanol (16 ml) was treated at room temperature with diethyl (ethoxymethylene)malonate (0.43 ml, 2.0 mmol) in ethanol (8 ml), and the mixture stirred for 2 hours. The solution was then neutralised with dilute hydrochloric acid (5N), concentrated by evaporation and the residue partitioned between ethyl acetate and saturated aqueous potassium carbonate solution. The aqueous layer was separated, acidified to pH 2 (5N hydrochloric acid) and extracted with ethyl acetate. Drying (sodium sulphate) and evaporation gave the title product (0.46 g, 74%), m.p. 225-6° (from methanol); i.r. (CH_2Cl_2): ν_{max} 1720 (weak), 1685, 1590, 1580, 1500, 1320, 1150 cm^{-1}; (Nujol): ν_{max} 3340, 3110, 1695, 1595, 1580, 1530, 1300, 1145 cm^{-1}; u.v. (EtOH): λ_{max} 300 nm (log ε 4.41); ^1H nmr [$(CD_3)_2SO$]: δ1.27 (3H, t, CH_3-C, J = 7 Hz), 3.20 (3H, s, CH_3SO_2-), 4.17 (2H, q, $-CH_2O-$, J = 7 Hz), 7.91 (4H, s, aryl protons), 8.83 (1H, s, pyrazolinone 3-proton). (Found: C, 50.31; H, 4.56; N, 8.99. Calc. for $C_{13}H_{14}N_2O_5S$: C, 50.31; H, 4.55; N, 9.03%).

4-Ethoxycarbonyl-1-p-(methylsulphonyl)phenyl-3-pyrazolin-5-one (3d) (direct preparation)

p-(Methylsulphonyl)phenylhydrazine (0.19 g, 1.0 mmol) in dry ethanol (10 ml) was treated with potassium carbonate (0.14 g, 1.0 mmol) and diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol), and the mixture stirred at reflux for two hours. The mixture was then cooled, concentrated by evaporation, and the residue partitioned between ethyl acetate and saturated potassium carbonate solution. The aqueous layer was separated, acidified to pH 2 (5N hydrochloric acid) and extracted with ethyl acetate. Drying (sodium sulphate) and evaporation gave the title product (0.27 g, 87%), m.p. 181-2° (from methanol); i.r. (CH_2Cl_2): ν_{max} 1720 (weak), 1660, 1585, 1575, 1320, 1150 cm^{-1}; (Nujol): ν_{max} 3330, 3110, 1680, 1595, 1575, 1500, 1300, 1145 cm^{-1}; u.v. (EtOH): λ_{max} 261 nm (log ε 4.40); ^1H nmr [$(CD_3)_2SO$]: δ 1.33 (3H, t, CH_3-C, J = 7 Hz), 3.29 (3H, s, CH_3SO_2-), 4.28 (2H, q, $-CH_2O-$, J = 7 Hz), 7.92 (1H, s, pyrazolinone 3-proton), 8.06 (4H, s, aryl protons). (Found: C, 50.15; H, 4.66; N, 8.91; S, 10.18. Calc. for $C_{13}H_{14}N_2O_5S$: C, 50.31; H, 4.55; N, 9.03; S, 10.33%).

4-Ethoxycarbonyl-1-p-(methylsulphonyl)phenyl-3-pyrazolin-5-one (3d) (preparation via isolation of intermediate 2-[2,2-bis(ethoxycarbonyl)ethenyl]-1-p-(methylsulphonyl)phenylhydrazine (2d))

p-(Methylsulphonyl)phenylhydrazine (0.19 g, 1.0 mmol) and diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol) with 3 drops 5N hydrochloric acid were heated in ethanol:tetrahydrofuran (1:1, 10 ml) at reflux for 1 hour. The solvent was evaporated and the residue partitioned between saturated aqueous potassium carbonate solution and ethyl acetate. The organic layer was shaken, separated, dried (sodium sulphate) and evaporated to give crude 2-[2,2-bis(ethoxycarbonyl)ethenyl]-1-p-(methylsulphonyl)phenylhydrazine (2d) which was chromatographed on silica (hexane:ethyl acetate [1:1]) (0.16 g, 45%). This gum was converted to the title product without further purification. It possessed i.r. (CH_2Cl_2): ν_{max} 3300 (br), 1700, 1660, 1600 cm^{-1}; u.v. (EtOH): λ_{max} 283 nm; ^1H nmr ($CDCl_3$): δ1.28, 1.34 (2 x 3H, 2t, $(CH_3-C)_2$, J = 7, 7 Hz), 2.98 (3H, s, CH_3SO_2-), 4.12, 4.22 (2 x 2H, 2q, $(-CH_2O)$, J = 7, 7 Hz), 6.77 (2H, d, aryl protons, J = 8.5 Hz), 7.50 (1H, s, -NHPh, exchanges with D_2O), 7.60 (2H, d, aryl protons, J = 8.5 Hz), 7.97 (1H, d, =CH-N-, J = 12 Hz, collapses to s with D_2O), 9.87 (1H, d, -NH-C=C-, J = 12 Hz, exchanges with D_2O).

2-[2,2-Bis(ethoxycarbonyl)ethenyl]-1-p-(methylsulphonyl)phenylhydrazine (2d) (0.135 g, 0.38 mmol) and potassium carbonate (0.055 g, 0.40 mmol) were added to dry ethanol (5 ml) and the mixture heated under reflux for 2 hours. After cooling the solution was concentrated and the residue partitioned between ethyl acetate and water. The aqueous layer was shaken, separated and acidified to pH 2 with dilute hydrochloric acid (5N). Extraction with ethyl acetate gave after drying (sodium sulphate) and evaporation, the title product (0.09 g, 77% from (2d)), identical to the material prepared as above directly from p-(methylsulphonyl)phenylhydrazine.

4-Ethoxycarbonyl-2-m-nitrophenyl-3-pyrazolin-5-one (4e)

m-Nitrophenylhydrazine hydrochloride (2.0 g, 10.5 mmol) was converted to the free hydrazine. This was dissolved in dry ethanol (50 ml) and sequentially treated with an ethanolic solution of 1M sodium ethoxide (22.2 ml) and diethyl (ethoxymethylene)malonate (2.18 ml, 10.1 mmol). The solution was stirred at room temperature under nitrogen for 3 hours, and then neutralised (5N hydrochloric acid) and concentrated by evaporation. The residue was diluted with water (100 ml) and the pH lowered to 2.5 (5N hydrochloric acid) whereupon a precipitate was produced. This mixture was extracted into ethyl acetate to give, after drying (magnesium sulphate) and evaporation, the title product (2.73 g, 97%), m.p. 175° (from ethyl acetate); i.r. ($CHCl_3$): ν_{max} 1725 (weak), 1685, 1600, 1585, 1535, 1515, 1355 cm^{-1}; (Nujol): ν_{max} 3120, 3200-2400, 1680, 1605, 1585, 1530, 1355 cm^{-1}; u.v. (EtOH): λ_{max} 283 nm (log ε 4.28); ^1H nmr [$(CD_3)_2CO$ + drop $(CD_3)_2SO$]: δ 1.34 (3H, t, CH_3C-, J = 7 Hz), 4.27 (2H, q, $-CH_2O$-, J = 7 Hz), 7.70 (1H, t, 5-phenyl proton, J = 8 Hz), 8.15 (2H, complex, aryl protons), 8.60 (1H, t, 2-phenyl proton, J = 2 Hz), 8.82 (1H, s, pyrazolinone 3-proton). (Found: C, 52.32; H, 3.89; N, 15.03. Calc. for $C_{12}H_{11}N_3O_5$: C, 51.99; H, 4.00; N, 15.16%).

4-Ethoxycarbonyl-1-m-nitrophenyl-3-pyrazolin-5-one (3e) (direct preparation)

To a solution of potassium carbonate (0.28 g, 2.0 mmol) and m-nitrophenylhydrazine (0.31 g, 2.0 mmol) (previously liberated from the hydrochloride) in water (20 ml) was added diethyl (ethoxymethylene)malonate (0.43 ml, 2.0 mmol), and the mixture stirred at reflux for 1.5 h. The mixture was cooled, washed with ethyl acetate and acidified to pH 2.5 (5N hydrochloric acid). The precipitate was extracted into ethyl acetate to give, after drying (magnesium sulphate) and evaporation, the title product (0.37 g, 67%), m.p. 154-5° (from ethyl acetate); i.r. ($CHCl_3$): ν_{max} 1730 (weak), 1665, 1600, 1585, 1540, 1515, 1355 cm^{-1}; (Nujol): ν_{max} 3230, 3140, 1670, 1660, 1590, 1535, 1350 cm^{-1}; [$(CD_3)_2SO$]: ν_{max} 1700 cm^{-1}; u.v. (EtOH): λ_{max} 247 nm (log ε 4.55); ^1H nmr [$(CD_3)_2SO$]: δ 1.42 (3H, t, CH_3C-, J = 7 Hz), 4.30 (2H, q, $-CH_2O$-, J = 7 Hz), 7.61 (1H, t, 5-phenyl proton, J = 8 Hz), 7.88 (1H, s, pyrazolinone 3-proton), 8.10 (2H, complex, aryl protons), 8.68 (1H, t, 2-phenyl proton, J = 2 Hz). (Found: C, 52.07; H, 3.84; N, 15.17. Calc. for $C_{12}H_{11}N_3O_5$: C, 51.99; H, 4.00; N, 15.16%).

4-Ethoxycarbonyl-1-m-nitrophenyl-3-pyrazolin-5-one (3e) (preparation via isolation of intermediate 2-[2,2-bis(ethoxycarbonyl)ethenyl]-m-nitrophenylhydrazine (2e))

m-Nitrophenylhydrazine hydrochloride (0.19 g, 1.0 mmol) was suspended in dry ethanol (10 ml) and treated with diethyl (ethoxymethylene)malonate (0.22 g, 1.0 mmol) and the mixture stirred at reflux under nitrogen for 3 hours. The reaction mixture was cooled, concentrated by evaporation and the residue partitioned between potassium carbonate solution and ethyl acetate. The organic layer was dried (magnesium sulphate) and evaporated to give a mixture (0.29 g) from which the intermediate **(2e)** was isolated after chromatography on silica (hexane:ethyl acetate (3:1)), (0.20 g, 63%), m.p. 120° (from chloroform:hexane); i.r. ($CHCl_3$): ν_{max} 1690, 1650, 1615, 1530, 1355 cm^{-1}; (Nujol): ν_{max} 3250, 1670, 1645, 1630, 1525, 1355 cm^{-1}; u.v. (EtOH): λ_{max} 278 nm (log ε 4.38); ^1H nmr ($CDCl_3$): δ 1.28, 1.33 (2 x 3H, 2t, $(CH_3-C)_2$, J = 7, 7 Hz), 4.13, 4.21 (2 x 2H, 2q, $(-CH_2O-)_2$, J = 7, 7 Hz), 7.54 (5H, complex, aryl protons and aryl NH-), 8.05 (1H, d, =CH-N-, J = 11 Hz, collapses to s with D_2O), 9.87 (1H, d, -NH-C=, J = 11 Hz, exchanges with D_2O). (Found: C, 51.99; H, 5.28; N, 12.78. Calc. for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00).

The intermediate **(2e)** (80 mg, 0.25 mmol) was dissolved in dry ethanol (5 ml) and treated with potassium carbonate (35 mg, 0.25 mmol). The mixture was stirred under nitrogen at reflux for 1 hour, cooled and water (10 ml) added. The solution was concentrated by evaporation, acidified to pH 2.5 (5N hydrochloric acid) and extracted with ethyl acetate to give, after drying (magnesium sulphate) and evaporation, the title product (65 mg, 93% from **(2e)**), identical to the material prepared directly from m-nitrophenylhydrazine.

4-Ethoxycarbonyl-2-p-nitrophenyl-3-pyrazolin-5-one (4f)

4-Ethoxycarbonyl-2-phenyl-3-pyrazolin-5-one (**4a**) (3.78 g, 16.3 mmol) in concentrated sulphuric acid (16 ml) was treated at 0° with nitric acid (d 1.42, 0.95 ml, 16.3 mmol) in concentrated sulphuric acid (16 ml). The mixture was stirred 1 hour at 0° and then added to an ice-water slurry (100 ml). The precipitate was filtered, washed with water and dried under vacuum. Recrystallisation gave the title compound (3.05 g, 67%), m.p. 190° (from ethanol); i.r. ($CHCl_3$): ν_{max} 3350, 1720 (weak), 1685, 1585, 1520, 1340 cm^{-1}; (Nujol): ν_{max} 3300-2500, 3140, 1685, 1590, 1525, 1505, 1345 cm^{-1}; u.v. (EtOH): λ_{max} 331 nm (log ε 4.33); ^1H nmr [$(CD_3)_2SO$]: δ1.32 (3H, t, CH_3C-, J = 7 Hz), 4.27 (2H, q, $-CH_2O$, J = 7 Hz), 8.09 (2H, d, aryl protons, J = 9.5 Hz), 8.40 (2H, d, aryl protons, J = 9.5 Hz), 9.06 (1H, s, pyrazolinone 3-proton). (Found: C, 52.23; H, 4.02; N, 14.87. Calc. for $C_{12}H_{11}N_3O_5$: C, 51.98; H, 4.00; N, 15.15%).

4-Ethoxycarbonyl-1-p-nitrophenyl-3-pyrazolin-5-one (3f)

p-Nitrophenylhydrazine (0.15 g, 1.0 mmol) and diethyl (ethoxymethylene)malonate (0.22 ml, 1.0 mmol) were dissolved in dry ethanol (10 ml) and the solution cooled to 0°. An ethanolic solution of sodium ethoxide (1M, 2.2 ml) was added and the mixture stirred under nitrogen at room temperature for 0.7 hours. The solution was diluted with water (30 ml) and acidified to pH 2.5 (5N hydrochloric acid). The resultant precipitate was filtered off, washed with water and dried under vacuum to give the title product (0.115 g, 42%), m.p. 198-9° (from ethyl acetate); i.r. ($CHCl_3$): ν_{max} 1730 (weak), 1670, 1610, 1585, 1520, 1345 cm^{-1}; [$(CH_3)_2SO$]: ν_{max} 1700 cm^{-1}; (Nujol): ν_{max} 3300-2500, 3125, 1670, 1600, 1580, 1515, 1340 cm^{-1}; u.v. (EtOH): λ_{max} 301 nm (log ε 4.17); ^1H nmr [$(CH_3)_2SO$]: δ1.35 (3H, t, CH_3C-, J = 7 Hz), 4.30 (2H, q, $-CH_2O$-, J= 7 Hz), 7.90 (1H, s, pyrazolinone 3-proton), 8.01 (2H, d, aryl protons, J = 9 Hz), 8.33 (2H, d, aryl protons, J = 9 Hz). (Found: C, 52.23; H, 4.00; N, 14.87. Calc. for $C_{12}H_{11}N_3O_5$: C, 51.98; H 4.00; N, 15.15%).

References

1. M.J. Basker, R.T. Cook, J. Lowther and A.W. Taylor, J. **Antibiotics**, **39**, 479 (1986).
2. L. Claisen and E. Haase, **Chem. Ber.**, **28**, 36 (1895).
3. C.C. Cheng and R.J. Robins, **J. Org. Chem.**, **21**, 1240 (1956).
4. G.H. Brown, B. Graham, P.W. Vittum and A. Weissberger, **J. Am. Chem. Soc.**, **73**, 919 (1951).
5. G.A. Newman and P.J.S. Pauwells, **Tetrahedron**, **25**, 4605 (1969).
6. G.A. Newman and P.J.S. Pauwells, **Tetrahedron**, **26**, 3429 (1970).
7. A. Michaelis and E. Remy, **Chem. Ber.**, **40**, 1020 (1907).
8. G. Desimoni, P.P. Righetti, E. Selva and G. Tacconi, **Tetrahedron**, **33**, 2829 (1977).
9. G. Ege and H. Franz, **J. Heterocyclic Chem.**, **19**, 1265 (1982).