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The reaction of diethyl (phthalimidoacetyl)malonate with hydroxylamine was investigated. Depending upon the reaction conditions, *N*-phthaloylglycinehydroxamic acid (**2**) and the cyclized product, 4-ethoxycarbonyl-5-hydroxy-3-(phthalimidomethyl)isoxazole (**4**), were obtained.

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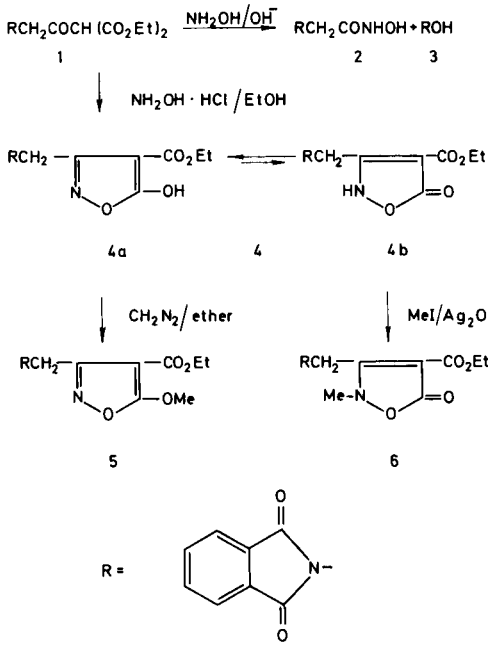
In a previous communication (1) the reaction has been described between diethyl (phthalimidoacetyl)malonate (**1**) and hydroxylamine under basic conditions, followed by immediate acidification.

Jacquier, *et al.*, (2) described the synthesis of 3-hydroxyisoxazoles using β-ketoesters substituted in the α-position and hydroxylamine under basic conditions followed by acidification. It was of interest to further investigate this reaction with β-keto-γ-phthalimidoesters, as a possible source of phthalimidoalkyl substituted 3-hydroxyisoxazoles.

The reaction of diethyl (phthalimidoacetyl)malonate with hydroxylamine is very sensitive to reaction conditions. We have now found that the reaction of diethyl (phthalimidoacetyl)malonate (**1**) with hydroxylamine under basic conditions proceeded with β-cleavage and hydroxylaminolysis, while no cyclization products were formed. The products, *N*-phthaloylglycinehydroxamic acid (**2**, 73%) and *N*-hydroxyphthalimide (**3**, 25%) were isolated from the reaction mixture. The structural assignments resulted from the spectral data. The mass spectrum showed a relatively strong parent ion at m/e 220. The intense M-32 peak undoubtedly arises from the cleavage of NHOH from hydroxamic acid (**2**). The nmr spectrum was consistent with the structure, while the ir spectrum exhibited absorption bands at 3310, 3210, and 1690 cm^{-1} characteristic of hydroxamic acids.



The structure of compounds **2** and **3** were unambiguously confirmed by comparison with samples prepared by an alternative route (3,4).

The cyclization of **1** can, however, be easily performed by reaction with hydroxylamine hydrochloride in ethanol at room temperature. 4-Ethoxycarbonyl-5-hydroxy-3-(phthalimidomethyl)isoxazole (**4**) was obtained in good yields. The compound gave a characteristic orange colour with ferric chloride solution and the spectral data were consistent with the 5-hydroxyisoxazole structure.

Compound **4** showed a comparatively weak parent ion at mass 316 and the base peak also appeared at m/e 160. Consequently, a closer parallel to the character of the fragmentation of **2** was found in the fragmentation of **4** itself. Prominent peaks also appeared at m/e 186 [$C_6H_4(CO)_2NCH_2CN^+$] and m/e 130 ($O_2CCHCO_2C_2H_5^+$), which might result from the simple cleavage of the isoxazole ring. The nmr absorption of hydrogen on the heteroatom occurred in a low field (δ 10.65) and was unaffected by dilution or solvent interaction, suggesting intramolecular hydrogen bonding. The infrared spectrum of **4** exhibited a band at 1690 cm^{-1} which is characteristic for an ester carbonyl being hydrogen-bonded to an isoxazol hydroxyl.

Treatment of 5-hydroxyisoxazole **4** with diazomethane in ether gave 4-ethoxycarbonyl-5-methoxy-3-(phthalimidomethyl)isoxazole (**5**) as colourless prisms in a 70% yield. When the silver salt of compound **4** was treated with methyl iodide, a mixture of *ca.* 30 per cent of 4-ethoxycarbonyl-2-methyl-3-(phthalimidomethyl)isoxazolin-5-one (**6**) and 20 per cent of the *O*-methyl derivative **5** was obtained.

The nmr spectrum of the *O*-methyl derivative **5** showed a sharp three-proton singlet at δ 4.19 and an intense ir absorption band at 1715 attributed to the ester carbonyl, while the *N*-methyl derivative **6** showed a singlet at δ 3.73 in the nmr, and two bands in the ir at 1760 and 1725 cm^{-1} due to cyclic and ester carbonyl stretching vibrations.

On the basis of spectral properties, as well as of the behaviour toward ferric chloride and methylating agents, the tautomeric hydroxyisoxazole structure **4a** appears to be the stable form. This apparently well-developed tendency for **4** to exist in the hydroxyisoxazole form is possibly due to stabilization by chelate hydrogen bonding

(5). No similar possibility existed in the discussed isoxazole derivatives lacking a carbonyl group in position 4 and which mostly appear to exist in their isoxazolin-5-one tautomeric forms.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-nmr spectra were recorded in DMSO-d_6 or deuteriochloroform solutions on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Coupling constants are expressed in c/s and multiplicity indicated as: s = singlet, d = doublet, t = triplet, q = quartet, umc = unresolved multiplet centre, b = broad. Infrared spectra were recorded on a Perkin-Elmer 257 instrument in potassium bromide pellets. The mass spectra were obtained on a Varian MAT CH-7 mass spectrometer at standard conditions. Thin layer chromatography (tlc) was carried out on Silica gel 60 F_{254} (Merck), solvent mixture benzene:ethyl acetate:formic acid (15:15:1).

N-Phthaloylglycinehydroxamic acid (**2**).

A stirred solution of hydroxylamine hydrochloride (0.695 g., 10.0 mmoles) and sodium hydroxide (0.8 g., 20.0 mmoles) in water (10 ml.) was cooled in an ice bath and a suspension of diethyl (phthalimidoacetyl)malonate (**1**, 3.47 g., 10.0 mmoles) in ethanol (15 ml.) was gradually added. Stirring was continued until the mixture became homogeneous, and was then diluted with water (3 ml.). After standing at 4° for 1 hour the mixture was acidified to *p*H 2 with concentrated hydrochloric acid and left at 4° for further 5 hours. The precipitate was collected, dried, and 1.6 g. of crude product was obtained which was shown by tlc to be a mixture containing two major constituents. Recrystallization from ethanol:water gave 1.6 g. (73%) of *N*-phthaloylglycinehydroxamic acid (**2**). The analytical sample was obtained by three additional recrystallizations from water, m.p. 189-190°; ir (potassium bromide): 3310 (vs), 3210 (s), 1775 (s), 1715 (vs), 1690 (vs), 1466 (s), 1427 (vs), 1400 (s), 960 (s), 717 (s) cm^{-1}; nmr (DMSO-d_6): δ 10.80, 8.90 (b, 2H, NHOH), 7.83 (umc, 4H, arom.), 4.17 (s, 2H, NCH_2); ms: m/e (relative intensity) 220 (12), 188 (12), 178 (4), 174 (2), 160 (100), 147 (1), 133 (8), 132 (5), 77 (16), 76 (17), 51 (9), 32 (15), 28 (57).

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.50; H, 3.63; N, 12.72. m.w. 220.18. Found: C, 54.48; H, 3.98; N, 12.75; m/e 220.

The mother liquor was extracted with a mixture of ether-petroleum ether (4:1, 3 x 10 ml.) and crude *N*-hydroxyphthalimide (**3**) was obtained from the extracts. Recrystallization from ethanol gave the pure product as fine colourless needles (400 mg., 25%) with the m.p. 228-230°. Mixed m.p. with authentic specimen: 229-230°; literature value 230°; ir (potassium bromide): 3400-2000 br, 1790 (ms), 1745 (s), 1710 (vs), 1610 (m), 1466 (ms), 925 (ms), 695 (s) cm^{-1}.

4-Ethoxycarbonyl-5-hydroxy-3-(phthalimidomethyl)isoxazole (**4**).

A suspension of diethyl (phthalimidoacetyl)malonate (3.47 g., 10 mmoles) and of hydroxylamine hydrochloride (0.695 g., 10 mmoles) in absolute ethanol (30 ml.) was stirred at room temperature. After stirring for 7 hours the suspension became clear and after 26 more hours a crystalline solid separated. The reaction mixture was diluted with ice-water (100 ml.) and extracted with dichloromethane (3 x 20 ml.). The combined extracts in which tlc showed the presence of starting material, were washed with water (5 x 50 ml.) and after removal of the water from the combined washings the 4-ethoxycarbonyl-5-hydroxy-3-(phthalimidomethyl)-isoxazole (**4**) was filtered off. The crude product was washed with dichloromethane and gave 1.8 g. (56%) of **4** as a pink solid product, m.p. 182-184°, which gave an orange colour with ferric chloride as spraying reagent. The analytical sample was prepared by three additional recrystallizations from methanol, pale pink rhombs, m.p. 194-195.5°; ir (potassium bromide): 3600-2300 br, 1780 (s), 1730 (vs), 1690 (vs), 1540 (s), 1412 (m), 1392 (s), 1376 (ms), 1350 (ms), 1190 (mw), 940 (ms), 717 (ms) cm^{-1}; nmr (DMSO-d_6): δ 10.65 (bs, 1H, hetero-H), 7.87 (umc, 4H, arom.), 4.88 (s, 2H, NCH_2), 4.13 (q, 2H, OCH_2, J = 7), 1.24 (t, 3H, CH_3, J = 7); ms: m/e (relative intensity) 316 (4), 300 (1), 288 (1), 270 (44), 244 (8), 228 (3), 226 (2), 212 (7), 198 (10), 186 (10), 184 (8), 176 (3), 171 (9), 160 (100), 148 (13), 147 (12), 143 (4), 142 (3), 133 (14), 132 (19), 130 (16), 105 (19), 104 (63), 77 (34), 76 (49).

Anal. Calcd. for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.82; N, 8.86; m.w. 316. Found: C, 56.66; H, 3.97; N, 9.13; m/e 316.

The dichloromethane layer and washings were combined and concentrated, yielding 1.2 g. of substance, mainly consisting of diethyl (phthalimidoacetyl)malonate (**1**).

4-Ethoxycarbonyl-5-methoxy-3-(phthalimidomethyl)isoxazole (**5**).

Compound **4** (0.365 g., 1.15 mmoles) was treated with ethereal diazomethane (prepared from 15 g. of nitrosomethylurea) at 0° until gas evolution ceased. The resulting reaction mixture was left overnight at the same temperature and then was concentrated to the half of its original volume. A crystalline solid separated, giving 0.27 g. (70%) of crude 4-ethoxycarbonyl-5-methoxy-3-(phthalimidomethyl)isoxazole (**5**), m.p. 151-154°. The analytical sample, m.p. 154-155°, was prepared by recrystallization from benzene-petroleum ether as colourless prisms; ir (potassium bromide): 1778 (ms), 1730, 1715 (vs), 1625, 1620 (s), 1540 (s), 1482 (ms), 1420, 1407 (ms), 1385 (s), 1118 (s), 950 (s), 717 (ms) cm^{-1}; nmr (deuteriochloroform): δ 7.79 (umc, 4H, arom.), 5.10 (s, 2H, NCH_2), 4.30 (q, 2H, OCH_2, J = 7), 4.19 (s, 3H, OCH_3), 1.37 (t, 3H, CH_3, J = 7).

Anal. Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48; m.w. 330. Found: C, 58.13; H, 4.00; N, 8.29.

4-Ethoxycarbonyl-2-methyl-3-(phthalimidomethyl)isoxazolin-5-one (**6**).

Compound **4** (0.316 g., 1 mmole) suspended in methanol was vigorously shaken at 25° for 2 hours with silver oxide (2 g.) and methyl iodide (1.25 ml.). Three further additions of silver oxide (2 g.) and methyl iodide (1.25 ml.) were made at intervals of 2 hours and shaking was continued for two more hours. The silver salts were removed by filtration and washed three times with hot methanol. Removal of methanol from the combined washings gave colourless residue from which the pure *O*-methyl derivative **5** was obtained (0.070 g., 20%). The filtrate was concentrated, and after standing overnight at 0° a crystalline solid separated giving 0.1 g. (30%) of 4-ethoxycarbonyl-2-methyl-3-(phthalimidomethyl)isoxazolin-5-one (**6**); m.p. 189.5-191°. The analytical sample was recrystallized from benzene giving **6** as colourless needles, m.p. 193-194°; ir (potassium bromide): 1785 (s), 1760 (vs), 1735 (vs), 1725 sh, 1570 (m), 1400 (s), 1347 (m), 1186 (m), 713 (s) cm^{-1}; nmr (deuteriochloroform): δ 7.79 (umc, 4H, arom.), 5.10 (s, 2H, NCH_2), 4.18 (q, 2H, OCH_2, J = 7.2), 3.73 (s, 3H, NCH_3), 1.28 (t, 3H, CH_3, J = 7.2).

Anal. Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48; m.w. 330. Found: C, 57.93; H, 3.97; N, 8.16.

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