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# Cyclization of Diethyl(phthalimidoacetyl)malonate into 3-(Phthalimidomethyl)pyrazolin-5-ones

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The cyclic parent (II) of the title series, and the following 1- or/and 4-substituted derivatives therefrom: 4-ethoxycarbonyl (III), 1-phenyl-4-ethoxycarbonyl (IV), and 1-phenyl (V), were prepared by conventional methods. (III) and (IV) gave each a single product on methylation with ethereal diazomethane. Structures of these products, and those of (II) — (V), are discussed on the basis of proton magnetic resonance and infrared spectra.

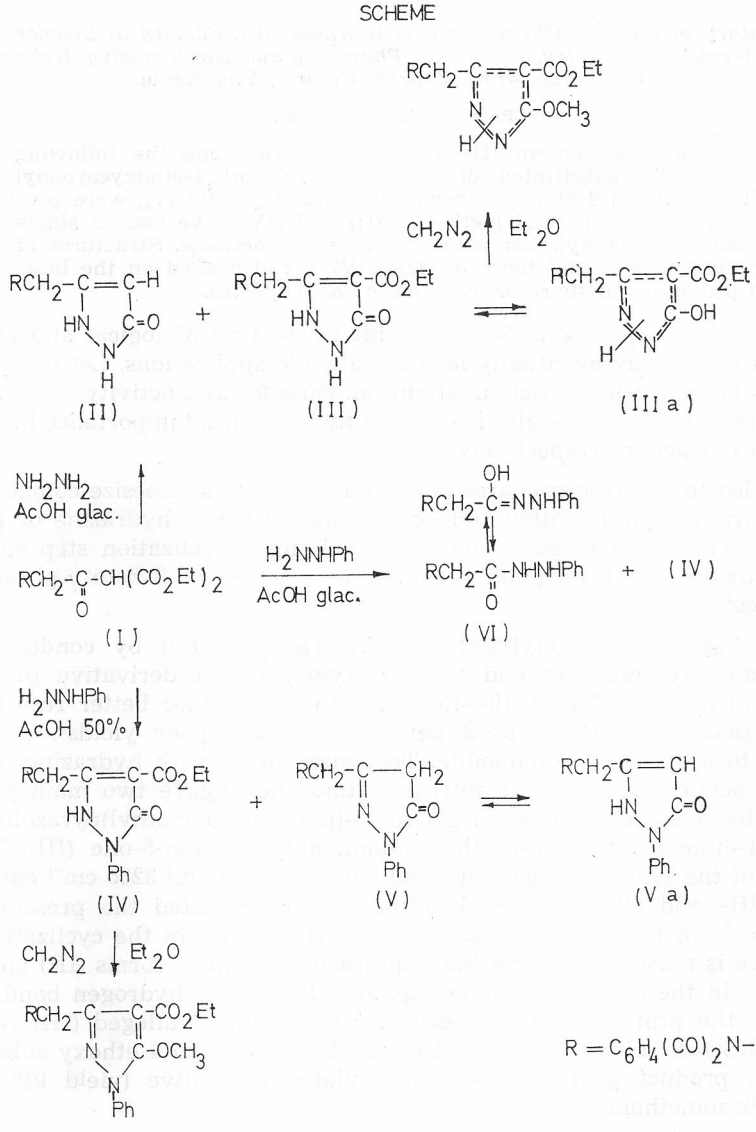
Derivatives of pyrazolin-5-one exhibit interesting biological and chemical properties which may eventually lead to valuable applications. Let two of these properties be called to particular attention: carcinostatic activity[1], and marked chelating power toward metals[2], because of their potential importance in therapy and metal extraction, respectively.

We wish to describe preparative methods used to synthesize compounds of this type from diethyl (phthalimidoacetyl) malonate and hydrazine or phenylhydrazine. The study of such methods involving a cyclization step continues our investigation of cyclization reactions in a series of β-keto-γ-phthalimido aliphatic esters[3].

Diethyl(phthalimidoacetyl)malonate (I) was prepared by condesation of phthalimidoacetyl chloride and the ethoxymagnesium derivative of diethyl malonate in dry benzene at 10—15 °C. By this procedure better results were obtained than by methods used before, that gave poor yields[4], and were reported[5] to be poorly reproducible. Treatment of (I) with hydrazine hydrate, in glacial acetic acid and in a nitrogen atmosphere, gave two main products differing by a 4-ethoxycarbonyl group: 3-(phthalimidomethyl)pyrazolin-5-one (II) and 4-ethoxycarbonyl-3-(phthalimidomethyl)pyrazolin-5-one (III). The IR spectrum of the latter product displayed bands at 3315 and 3265 $cm^{-1}$ characteristic of NH- and OH-hydrogen bonding, which indicated the presence of a tautomeric 5- or (3)-hydroxypyrazole ring system (IIIa) in the cyclization product. There is reason to believe that equilibrium between forms (III) and (IIIa) exists only in the solid state, as no signal indicative of hydrogen bonding appeared on the proton magnetic resonance spectrum of alleged (III) recorded with a DMSO-$d_6$ solution of the substance. However, the 4-ethoxy substituted cyclization product gave only one methylated derivative (yield 91%) with ethereal diazomethane.

When (I) was reacted with phenylhydrazine in 50% aqueous acetic acid two products resulted differing by a 4-ethoxycarbonyl group, similarly as with hydrazine. The two products were 4-ethoxycarbonyl-1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one (IV) and 1-phenyl-3-(phthalimidomethyl)pyrazolin-5--one (V). These compounds were previously prepared by Bradshaw et al.[6], who used either diethyl (phthalimidoacetyl)malonate or ethyl(phthalimidoacetyl)acetate as starting materials. In an attempt to react diethyl (phthalimidoacetyl)malonate and phenylhydrazine in glacial acetic acid, we obtained (IV) as the main product, but additionally, phthalimidoacetyl hydrazide (VI) was formed as side product (26%).

SCHEME



The $^1$H-NMR spectrum of alleged 1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one, recorded from a solution in DMSO-$d_6$, suggested that the CH-form (V) (i. e. 4H-form) was largely predominant, and only about 20% was present in the NH-form (Va).

Similarly as with (III), only a single methylated derivative was obtained by treating (IV) with ethereal diazomethane (yield 98%). This product, and the methylated derivative of (III), are depicted as *O*-methyl rather than *N*-methyl forms in the Scheme. The site of methyl substitution is, however, uncertain, as no comparable *N*-methyl derivatives are available to help to clear this point.

For convenience, NMR data characteristic of compounds (II)—(V) and the methylated derivatives of (III) and (IV), are summarized in Table. They are also given later (Experimental Section), along with pertinent IR data.

## EXPERIMENTAL

*General.* — All mp's are uncorrected. $^1$H-NMR and ir spectra were recorded on a Varian T-60 and a Perkin-Elmer M-137 instrument, respectively. NMR spectrometry was carried out in dimethylsulfoxide-$d_6$ and deuterochloroform solutions, with tetramethylsilane as the internal standard. IR recordings were made with KBr pellets.

*3-(Phthalimidomethyl)pyrazolin-5-one* (II) *and 4-ethoxycarbonyl-3-(phtalimidomethyl)pyrazolin-5-one* (III). — Diethyl (phthalimidoacetyl)malonate (3.47 g, 0.01 mol), glacial acetic acid (16 ml), and hydrazine hydrate (0.5 g, 0.01 mol), were heated 3 h at 95—100 °C while passing a stream of nitrogen through the vessel. Thereupon the solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (40 ml). The solution was washed with water (20 ml), and the organic and aqueous layers were separated.

On cooling crude 3-(phthalimidomethyl)pyrazolin-5-one separated from the aqueous phase (0.9 g, 37%), m. p. 285—290 °C which was purified by crystallization from ethanol-water: colorless prisms, m. p. 296—298 °C (dec.).

$^1$H-NMR spectrum (DMSO-$d_6$), $\delta$ values: 4.72 ppm (s, 2H, N—$CH_2$C); 5.40 ppm (s, 1H, vinyl H); 7.88 ppm (s, 4H, aromatic); 10.60 ppm (broad signal, 2H, HN—NH).

IR (KBr): 3380 s (NH, hydrazo group); 1770, 1725, 1715 s (phthalimido —C=O, ring —C=O); 1585 s (ring —C=C—); 3100—2600 cm$^{-1}$ many maxima in this range give evidence of NH/—OH hydrogen-bonding.

*Anal.* $C_{12}H_9N_3O_3$ (243.222) calc'd.: C 59.26; H 3.73; N 17.28%
found: C 59.42; H 3.95; N 17.39%.

From the organic phase separated 4-ethoxycarbonyl-3-(phthalimidomethyl)pyrazolin-5-one (1 g, 31%), m. p. 212—214 °C. Recrystallization from methanol gave white needles and raised the m. p. to 214—217 °C.

$^1$H-NMR spectrum (DMSO-$d_6$), $\delta$ values: 1.30 ppm (t, 3H, —$CH_2$—$CH_3$); 4.25 ppm (q, 2H, —$CH_2CH_3$); 4.94 ppm (s, 2H, >N—$CH_2$—C); 7.70 ppm (s, 4H, aromatic).

IR (KBr): 3405 m (NH, hydrazo group); 3315 s, 3265 s (NH— and OH— hydrogen-bonding in the tautomeric 5- or (3)-hydroxypyrazole ring IIIa); 1775, 1725, 1720, 1670 (phthalimido —C=O, ring —C=O and ester —C=O); 1582 m and 1538 cm$^{-1}$ s (—C=N and —C=C— respectively).

*Anal.* $C_{15}H_{13}N_3O_5$ (315.284) calc'd.: C 57.14; H 4.15; N 13.33%
found: C 57.20; H 4.08; N 13.44%.

The dichloromethane filtrate was left overnight at 0 °C, during which period needles (0.32 g, 11%) of ethyl (phthalimidoacetyl)acetate separated (mixed m. p. with an authentic sample was 110 °C; lit.[4], 110 °C).

Compound (III) (0.63 g, 2 mmol) was treated with ethereal diazomethane (prepared from 30 g of nitroso methyl urea) at O °C until gas evolution ceased, and the resulting solution was left overnight at the same temperature. A crystalline solid separated (0.3 g, m. p. 170—172 °C) and was collected by filtration. The ether was evaporated under reduced pressure to one-half the original volume, whereupon a second crop of crystals (0.3 g) was obtained (total yield 91%). Crystallization from methanol gave long white needles of the methylated product, m. p. 174—176 °C.

TABLE

*$^1H$ NMR Spectra of 3-(Phthalimidomethyl)pyrazolin-5-ones*

| Compound | Chemical shifts* | | | | | | Solvent |
|---|---|---|---|---|---|---|---|
| | 3-Substituent | | | 4-Substituent | 2- or 5-Substituent | Ring | |
| | Ar | | —$NCH_2$— | —CO—$OCH_2CH_3$ | | | |
| II | $C_6H_4(CO)_2N$ | 7.88 (s,4H) | 4.72 (s,2H) | | | C=CH 5.40 (s,1H)<br>NHNH 10.6 (broad,2H) | DMSO-$d_6$ |
| III | $C_6H_4(CO)_2N$ | 7.70 (s,4H) | 4.94 (s,2H) | 1.30 (t,3H)<br>4.25 (q,2H) | | | DMSO-$d_6$ |
| Methylated derivative of (III) | $C_6H_4(CO)_2N$ | 7.75 (m,4H) | 5.13 (s,2H) | 1.37 (t,3H)<br>4.32 (q,2H) | —$CH_3$ 3.90 (s,3H) | —NH— 10.50 broad,1H) | $CDCl_3$ |
| (IV) | $C_6H_4(CO)_2N$<br>$C_6H_5$ | 7.56—7.96 (m,4H)<br>7.1 —7.4 (m,5H) | 5.80 (s,2H) | 1.37 (t,3H)<br>4.38 (q,2H) | 7.56—7.96 (m,1H) | | $CDCl_3$ |
| (V) | $C_6H_4(CO)_2N$<br>$C_6H_5$ | 7.2 —8.1 (m,9H) | 4.77 (s,2H) | | | C=CH 5.53 (s,0.2H)<br>—$CH_2$— 3.30 (s,1.6H)<br>NH— 3.40 (s,0.2H) | DMSO-$d_6$ |
| Methylated derivative of (IV) | $C_6H_4(CO)_2N$<br>$C_6H_5$ | 7.68—7.98 (m,4H)<br>7.22—7.61 (m,5H) | 5.20 (s,2H) | 1.43 (t,3H)<br>4.40 (q,2H) | —$CH_3$ 4.07 (s,3H) | | DMSO-$d_6$ |

* Expressed as ppm downfield from internal TMS

$^1$H-NMR spectrum ($CDCl_3$), $\delta$ values: 1.37 ppm (t, 3H, —$CH_2$—$CH_3$); 3.90 ppm (s, 3H, —$CH_3$); 4.32 ppm (q, 2H, —$CH_2$—$CH_3$); 5.13 ppm (s, 2H, =N—$CH_2$—C); 7.75 ppm (m, 4H, aromatic); 10.50 ppm (broad signal, 1H, NH).

IR (KBr): 3430 s (NH); 1770, 1705 s, 1690 (phthalimido —C=O, ester —C=O); 1580 s and 1528 $cm^{-1}$ s.

*Anal.* $C_{16}H_{15}N_3O_5$ (329.310) calc'd.: C 58.36; H 4.59; N 12.76%
found: C 58.28; H 4.34; N 12.81%.

*4-Ethoxycarbonyl-1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one* (IV) *and 1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one* (V). — Diethyl (phthalimidoacetyl)malonate (3.47 g, 0.01 mol) and phenylhydrazine (1.1 g, 0.01 mol) were suspended in 50% acetic acid (10 ml), and the mixture was vigorously shaken. After a few minutes the mixture warmed up spontaneously and became homogenous. The reaction was completed by heating on a steam bath for 30 min.

The separated solid was collected and recrystallized from glacial acetic acid to obtain crude 4-ethoxycarbonyl-1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one (1.9 g, 48%), m. p. 211—213 °C. Recrystallization of this product from ethyl acetate gave colorless needles, m. p. 213—215 °C (reported[6] 215 °C).

$^1$H-NMR spectrum ($CDCl_3$), $\delta$ values: 1.37 ppm (t, 3H, —$CH_2$—$CH_3$); 4.38 ppm (q, 2H, —$CH_2$—$CH_3$); 5.80 ppm (s, 2H, N—$CH_2$—C); 7.13—7.43 ppm (m, 5H, —$C_6H_5$); 7.56—7.96 ppm (m, 4H + 1H, aromatic and hidrogen bonded.

IR (KBr): 3250 s; 1775, 1715 s (phthalimido —C=O); 1675 s (ester —C=O); 1592 s and 1568 s $cm^{-1}$.

*Anal.* $C_{21}H_{17}N_3O_5$ (391.376) calc'd.: C 64.45; H 4.37; N 10.74%
found: C 64.58; H 4.39; N 10.51%.

The mother liquor was concentrated to one-half its original volume. On cooling, crude 1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one separated (0.9 g, 28%), m. p. 190—192 °C. After recrystallization from methanol the compound formed colorless needles, m. p. 194—196 °C (reported[6] 192 °C).

$^1$H-NMR spectrum (DMSO-$d_6$), $\delta$ values: 3.30 ppm (s, 1.6 H, C—$CH_2$—C=C); 3.40 ppm (broad signal s, 0.2H, NH); 4.77 ppm (s, 2H, N—$CH_2$—C); 5.53 ppm (s, 0.2 H, vinyl H); 7.20—8.09 ppm (m, 9H, aromatic).

IR (KBr): 1780, 1725, 1715 (phthalimido —C=O and —C=O pyrazolon ring); 1595 s (C=N) $cm^{-1}$.

The methylated derivative of (IV) was prepared by the same procedure as that of (III), using 0.41 g (1.1 mmol) of (IV) and diazomethane prepared from 15 g of nitroso methyl urea. After removing of ether under reduced pressure 0.4 g (98%) of crude product, m. p. 180—183 °C, was obtained which, on crystallization from ethyl acetate, gave long white needles of the methylated derivative of (IV), m. p. 184—186 °C.

$^1$H-NMR spectrum ($CDCl_3$), $\delta$ values: 1.43 ppm (t, 3H, —$CH_2$—$CH_3$); 4.07 ppm (s, 3H, —$CH_3$); 4.40 ppm (q, 2H, —$CH_2$—$CH_3$); 5.20 ppm (s, 2H, N—$CH_2$—C); 7.22—7.61 ppm (m, 5H, $C_6H_5$); 7.68—7.98 ppm (m, 4H, aromatic).

IR (KBr): 1778, 1720, 1705 (phthalimido —C=O and ester C=O); 1598 s and 1566 $cm^{-1}$ s.

*Anal.* $C_{22}H_{19}N_3O_5$ (405.40) calc'd.: C 65.18; H 4.72; N 10.37%
found: C 65.00; H 4.50; N 10.50%.

*Phthalimidoacetyl phenylhydrazide* (VI). — Diethyl (phthalimidoacetyl)malonate (3.47 g, 10 mmol), glacial acetic acid (0.6 ml), and phenylhydrazine (1.2 g, 11 mmol), were heated at 100 °C for 30 min. The mixture was allowed to cool to room temperature, then water (20 ml) was added. On standing, crude 4-ethoxycarbonyl-1-phenyl-3-(phthalimidomethyl)pyrazolin-5-one, m. p. 211—213 °C, was precipitated (1.9 g, 48%). Recrystallization from ethyl acetate gave colorless needles, m. p. 213—215 °C. This product had an IR spectrum identical with that of (IV).

The filtrate was evaporated to one-half its original volume whereupon, on cooling, phthalimidoacetyl phenylhydrazide separated (0.77 g, 26%), m. p. 194—196 °C. Crystallization from methanol gave colorless needles, m. p. 196—8 °C (reported[6] 199 °C).

$^1$H-NMR spectrum (DMSO-$d_6$) $\delta$ values: 3.5 ppm (broad signal, 1H, =N—NH—); 4.40 ppm (d, 2H, N—$CH_2$—C); 6.62—7.36 ppm (m, 5H, —$C_6H_5$); 7.90 ppm (s, 4H, aromatic); 10.00 ppm (s, 1H, —OH enolic).

IR (KBr): 3360 s, 3325 (—NHNHPh); 1780 s, 1715 s (phthalimido —C=O); 1690 $cm^{-1}$ s (hydrazide —C=O).

*Anal.* $C_{16}H_{13}N_3O_3$ (295.294) calc'd.: C 65.08; H 4.44; N 14.23%
found: C 65.45; H 4.80; N 13.90%.

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## SAŽETAK

### Ciklizacija dietil(ftalimidoacetil)malonata u 3-(ftalimidometil)pirazolin-5-one

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Opisane su sinteze cikličkog spoja (II) reda pirazolin-5-ona te 1- i 4-supstituiranih derivata, i to: 4-etoksikarbonil (III), 1-fenil-4-etoksikarbonil (IV), i 1-fenil (V). Djelovanjem diazometana u eteru priređeni su metilirani derivati spoja (III) i (IV). Strukture opisanih spojeva razmatrane su na osnovi podataka dobivenih iz spektara $^1$H-nuklearne magnetske rezonancije, kao i infracrvenih spektara.

ZAVOD ZA ORGANSKU KEMIJU I BIOKEMIJU
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