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3-(Phthalimidoalkyl)-substituted Pyrazolin-5-ones

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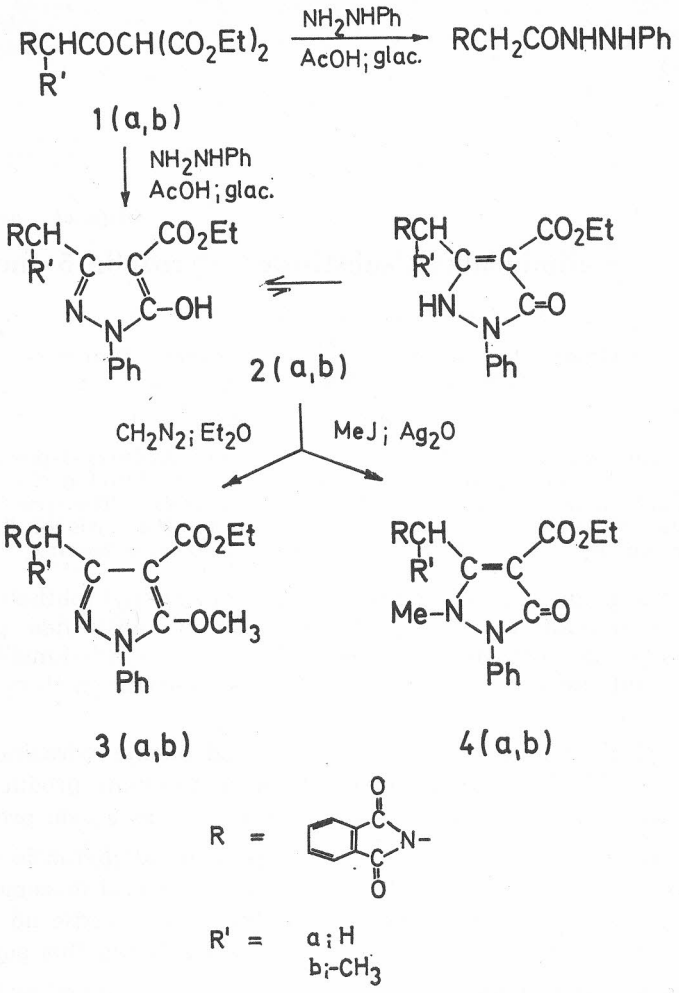
The syntheses of the 4-ethoxycarbonyl-5-hydroxy-1-phenyl--3-(α-phthalimidoethyl)pyrazole (*2b*), and its *O*-methyl derivative *3b*, as well as *N*-methyl derivative *4a*, are described. The structure of the obtained compounds are discussed on the basis of their infrared, mass and ^{1}H nuclear magnetic resonance spectra.

In continuing our research on the cyclization of diethyl (phthalimidoacetyl) malonate into derivatives of 3-(phthalimidomethyl)-substituted pyrazolin-5--ones[1] we have examined the cyclization of diethyl (α-phthalimidopropionyl)-malonate (*1b*) into analogues of pyrazolin-5-ones occurring in three tautomeric forms[2,3].

Diethyl (phthalimidoacetyl)malonate (*1a*)[1] and phenylhydrazine, in glacial acetic acid, gave the cyclization compound (*2a*) as the main product, but some phthalimidoacetyl hydrazide was additionally formed as a side product.

4-Ethoxycarbonyl-5-hydroxy-1-phenyl-3-(phthalimido)pyrazole (*2a*) gave a single methyl derivative (*3a*) in a 90% yield with ethereal diazomethane. The site of methyl substitution was uncertain at the time, because no comparable N-methyl derivative *4a* was available to help in clarifying this point.

In this paper we present a *N*-methyl derivative *4a*, obtained by treating the silver salt of *2a* with methyl iodide. This reaction gave two products, the *O*--methyl derivative *3a* in a 50% yield, and *N*-methyl derivative *4a* in a 20% yield .The basis of the use of NMR for determining these two methylated derivatives was the measurement of the chemical shift of the methyl group protons. The *N*-methyl group protons give a signal at higher field than the O-methyl group protons. On the ^{1}H-NMR spectrum of the 4-ethoxycarbonyl--1-phenyl-2-methyl-3-(phthalimidomethyl)pyrazolin-5-one (*4a*) a sharp three--proton singlet occured at δ 3.43 ppm, and the IR spectrum exhibited a strong broad band at 1725—1690 cm^{-1} due to cyclic and ester carbonyl stretching vibrations, respectively. On the basis of the ^{1}H-NMR spectrum of the 4-ethoxy--carbonyl-5-methoxy-3-(phthalimidomethyl)pyrazole (*3a*) a sharp three-proton singlet occured at δ 4.07. The IR spectrum of the tautomeric compound *2a* closely resembles that of the *O*-methyl-, and is different from that of the *N*-methyl analogue.



In the present paper we have described the cyclization of diethyl (α-phthalimidopropionyl)malonate (*1b*) into the analogue of pyrazolin-5-one.

The cyclization of *1b* can be easily performed by reaction with phenylhydrazine in glacial acetic acid and the only product obtained was the cyclization compound *2b* in a satisfactory yield. The spectral data of compound *2b* are consistent with the 5-hydroxypyrazole structure, and in reaction of this compound with ferric chloride a characteristic purple colour was observed. The mass spectrum of *2b* showed the parent ion at *m/e* 405 and the doubly charged molecular ion appeared at mass 202.5. From the occurence of significant metastable peak at 318.3, 305.3, 277.5, and 124.2 masses it follows that a multistep decomposition of parent ion *m/e* 405 → *m/e* 359 → *m/e* 331 → *m/e* 303, and *m/e* 174 → *m/e* 147 takes place. The ortho effect in *2b* is responsible for the preferential rearrangement of type E_2 which afforded the base peak at *m/e* 359 by elimination of ethanol. The NMR spectrum exhibited a marked downfield

shift of α-methyl protons (δ 1.92) attributed to anisotropic deshielding by the pyrazole system in the preferred conformation. Moreover, the chemical shifts of α-methyls in *2b* and corresponding *O*-methyl derivative *3b* were similar. The NMR absorption of exchangeable hydrogen (δ 10.43) was unaffected by dilution or solvent interaction, indicating intramolecular hydrogen bonding. The strong hydrogen bonding is also apparent from the infrared spectra of *2b*. The solid phase and chloroform spectra showed an intense band at 1665 cm^{-1} unaffected by dilution, characteristic of aromatic *O*-hydroxy esters. The low frequency shift of the ester carbonyl stretching (1715 cm^{-1}) was observed in the *O*-methyl derivative *3b* indicating a chelated structure *2b*.

The crystal and molecular structure of compound *2b* was solved by use of direct methods (Multan program) and Fourier synthesis[4]. The most characteristic feature of the structure is a strong intramolecular O—H . . . O hydrogen bond of 2.694 Å.

Reaction of 5-hydroxypyrazole *2b* with diazomethane in ether gave 4--ethoxycarbonyl-5-methoxy-1-phenyl-3-(α-phthalimidoethyl)pyrazole (*3b*) in a 76% yield. The NMR spectrum showed a sharp three proton singlet of the methoxy protons (δ 4.00), and two intense IR absorption bands at 1780 and 1725 cm^{-1}, attributed to phthalimido and ester carbonyl stretching vibrations. All attempts to obtain 4-ethoxycarbonyl-1-phenyl-2-methyl-3-(phthalimidoethyl) pyrazole (*4b*) by treating the silver salt of *2b* with methyl iodide ended in failure. The same compound *3b* was isolated as the only product, in a 30% yield. The bulky group in the 3-position of the pyrazole ring in *2b* introduces a substantial hindrance to *N*-methylation, which may explain the exclusive formation of the *O*-methyl derivative on treatment with methyl iodide.

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 with deutero-chloroform solutions, using tetramethylsilane as the internal standard. IR spectra were recorded with KBr pellets.

Diethyl (α-phthalimidopropionyl)malonate (1b) was prepared by K. Adank's method.[5]

4-Ethoxycarbonyl-5-hydroxy-1-phenyl-3-(α-phthalimidoethyl)pyrazole (2b). — Diethyl (α-phthalimidopropionyl) malonate (3.6 g, 10 mmol) was heated on a steam bath with phenylhydrazine (1.1 g, 10 mmol) in glacial acetic acid (10 cm^3) for 30 min. The separated solid was collected, then dried, giving 3.0 g (77%) of crude 4-ethoxycarbonyl-5- hydroxy-1-phenyl-3-(α-phthalimidoethyl)pyrazole, m. p. 175—179 °C. The analytical sample m. p. 185—187 °C, was prepared by recrystallization from ethyl acetate as a colourless needles.

Mass spectrum, *m/e* (relative intensity): 406 (3.0), 405 (14.0), 359 (100.0), 344 (4.0), 332 (9.0), 331 (37.5), 303 (3.0), 227 (2.0), 213 (5.3), 212 (6.4), 211 (4.1), 199 (2.1), 198 (7.6), 186 (2.1), 185 (2.6), 184 (4.3), 175 (2.7), 174 (22.8), 148 (2.2), 147 (5.4), 133 (2.6), 132 (3.1), 131 (2.1), 130 (21.7), 105 (19.6), 104 (16.3), 97 (2.7), 93 (3.3), 92 (4.9), 91 (11.9), 81 (5.4), 77 (35.8), 76 (5.9), 69 (2.1), 65 (3.1), 53 (3.0), 51 (3.1).

^{1}H-NMR spectrum ($CDCl_3$), values δ 10.43 (br, 1H, OH, exchangeable with D_2O), 7.57 (umc, 9H, arom.), 5.71 (q, 1H, $CHCH_3$, J = 7.0 Hz), 4.18 (q, 2H, OCH_2CH_3, J = 7.5 Hz), 1.92 (d, 3H, $CHCH_3$, J = 7.0 Hz), 1.13 (t, 3H, OCH_2CH_3, J = 7.5 Hz).

IR(KBr); 1780, 1715, 1665, 1575, 1395, 1355, 1208, 1135, 725 cm^{-1}. The spectrum in $CHCl_3$ showed no appreciable changes.

Anal. $C_{22}H_{19}N_3O_5$ (405,396) calc'd: C 65.18; H 4.72; N 10.37%
found: C 65.33; H 5.02; N 10.62%

4-Ethoxycarbonyl-5-methoxy-1-phenyl-3-(α-phthalimidoethyl)pyrazole (3b). — Compound *2b* (0.420 g, 1.03 mmol) was treated with ethereal diazomethane (prepared from 15 g. of nitrosomethylurea) at 0 °C until gas evolution ceased. The resulting reaction mixture was left overnight at the same temperature. After removal of solvent under reduced pressure, residual 4-ethoxycarbonyl-5-methoxy-1-phenyl-3-(α-phthalimidoethyl)pyrazole was crystallized from ether — petroleum ether, m. p. 121—122 °C (0.33 g, 76%) yield).

^{1}H-NMR spectrum ($CDCl_3$), values δ 7.53 (umc, 9H, arom.), 5.90 (q, 1H, $CHCH_3$, J = 7.0 Hz), 4.25 (q, 2H, OCH_2CH_3, J = 7.5 Hz), 4.00 (s, 3H, OCH_3), 1.93 (d, 3H, $CHCH_3$, J = 7.0 Hz), 1.25 (t, 3H, OCH_2CH_3, J = 7.5 Hz).

IR (KBr): 1780, 1720, 1553, 1503, 1487, 1390, 1353, 1337, 1112, 720 cm^{-1}.

Anal. $C_{23}H_{21}N_3O_5$ (419.422) calc'd: C 65.85; H 5.05; N 10.02%
found: C 65.84; H 5.28; N 10.10%

The same methoxy compound *3b* was obtained in a 30% yield by treatment of the neutral silver salt of 3-(α-phthalimidoethyl)-substituted pyrazole *2b* with methyl iodide. This methoxy compound m. p. 120—121 °C, after two crystallizations from ether-petroleum ether, had the same IR spectrum as the product prepared from *2b* using ethereal diazomethane. The mixed m. p. of a mixture of samples *3b* was 120—122 °C.

4-Ethoxycarbonyl-1-phenyl-2-methyl-3-(phthalimidomethyl) pyrazolin-5-one (4a). — Compound *2a* (1.17 g, 3 mmol) and silver oxide (2.5 g) were suspended in methanol (30 cm^3), methyl iodide (3.75 cm^3) was added, and the mixture was vigorously shaken at room temperature for 2 hours. Three further additions of silver oxide (2.5 g) and methyl iodide (3.75 cm^3) were made at 2 hours intervals, and shaking was continued for 20 hours, after the last addition. The silver salts were removed by filtration and washed three times with hot methanol. The combined filtrate and washings were concentrated, and after standing overnight at —4 °C, 0.62 g (50%) of O-methyl derivative *(3a)* separated as a crystalline solid. The mother-liquor was evaporated to dryness in vacuo leaving an oily product. Recrystallization from benzene petroleum ether gave 0.25 g (20%) of 4-ethoxy-carbonyl-1-phenyl-2-methyl-3-(phthalimidomethyl)pyrazolin-5-one *4a* m. p. 245—247 °C. The analytical sample was recrystallized from methanol, giving a colourless product, m. p. 247—249 °C.

^{1}H-NMR spectrum ($CDCl_3$), δ values 7.78 (umc, 9H, arom), 5.27 (s, 2H, N-CH_2), 4.34 (q, 2H, CH_2CH_3), 3.43 (s, 3H, N-CH_3), 1.32 (t, 3H, CH_2CH_3).

IR (KBr): 1765, 1725—1690, 1525, 1400, 1350, 1176, 723 cm^{-1}.

Anal. $C_{22}H_{19}N_3O_5$ (405.40) calc'd.: C 65.18; H 4.72; N 10.37%
found: C 65.07; H 4.70; N 10.05%.

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SAŽETAK

3-(Ftalimidoalkil)-substituirani pirazolin-5-oni

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Pripravljeni su 4-etoksikarbonil-5-hidroksi-1-fenil-3-(α-ftalimidoetil)pirazol(*2b*), kao i O-metil derivat *3b*, te N-metil derivat *4a*. Strukture dobivenih spojeva razmatrane su na temelju infracrvenih i masenih spektara te spektara ^{1}H-nuklearne magnetske rezonancije.

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