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Preparation and Cyclization of Some β-Keto-γ-Phthalimidoaliphatic Esters

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The preparation of (α-phthalimidoacyl)malonates *via* mixed anhydrides (IIa, b) and subsequent monodeethoxycarbonylation into the (α-phthalimidoacyl)acetates (IVa, b) is described. Cyclization of (IIIa) with hydroxylamine led to 3-(phthalimidomethyl)isoxazolin-5-one-4-carboxylic acid (VI), while the malonate derivative (IIIb), when reacted with hydrazine, gave 4-ethoxycarbonyl-3-(α-phthalimidoethyl)pyrazolin-5-one (VII). The ketalization of ethyl (phthalimidoacetyl)acetate (IVa) with methyl orthoformate gave methyl (phthalimidoacetyl)acetate dimethyl ketal (V). The structure of the obtained compounds is discussed on the basis of their ^{1}H nuclear magnetic resonance spectra, in some cases supported by infrared data.

Isolation of biologically active substances from *Amanita muscaria* has stimulated the interest in the chemistry of 3-hydroxysoxazoles.[1] Muscimol, 3-hydroxy-5-aminomethylisoxazole, isolated from *A. muscaria* has shown remarkable and multiple biological activity particularly on human central nervous system provoking psychogenic effect[2]. Brehm *et al.*[3] have confirmed the isoxazole enolbetainic structure of muscimol by X-ray crystallographic methods. Gagneux *et al.*[4] described the synthesis of 3-hydroxy-5-chloromethylisoxazole from methyl γ-chloroacetyl acetate *via* the corresponding dimethyl ketal and hydroxylamine. Jacquier *et al.*[5] described the preparation of the derivatives of 3-hydroxyisoxazoles from ethylene ketal of appropriate β-ketoesters and hydroxylamine. They stated[6] that the relative amounts of the concerned 3-hydroxyisoxazoles and the isomeric isoxazolin-5-ones strongly depend on the constitutions of the β-ketoesters.

Recently Krogsgaard-Larsen *et al.*[7] reinvestigated the reaction between β-ketoesters, protected at a keto group with benzylamine, and hydroxylamine. In contrary to the earlier results[8], they have found that the same reactions afforded isoxazolin-5-ones, exclusively. The same authors showed that the method is of general value for the preparation of isoxazolin-5-ones.

It was of interest to investigate further the cyclization of β-keto-γ-phthalimidoesters, as a source of some highly substituted 3-hydroxyisoxazoles.

K. Adank *et al.*[9] described the synthesis of d,l-phthalimidoacyl-β-dicarbonyl compounds. They acylated ethoxy magnesium β-dicarbonyl derivatives with acid chlorides of N-phthaloylamino acids. The use of this method was

applied in 1961[10] for the preparation of diethyl (phthalimidoacetyl)malonate in 63% and ethyl (phthalimidoacetyl-acetate in 62% yield. In our case, however, the reinvestigation of this procedure resulted with 30% yield for both compounds.

In the present paper we described the acylation of diethyl ethoxy magnesium malonate with mixed anhydrides (IIa, b), prepared from *N*-phthaloylglycine and *N*-phthaloylalanine, respectively, and ethyl chloroformate. In this way the synthesis of (α-phthalimidoacyl)malonates (IIIa, b) and subsequent monodeethoxycarbonylation into (α-phthalimidoacyl)acetates (IVa, b) is performed in 35—40% yields.

Scheme I

$C_6H_4(CO)_2NCH(R)CO_2H + ClCO_2Et + Et_3N \rightarrow Et_3N \cdot HCl$
(Ia, b)

$C_6H_4(CO)_2NCH(R)CO{-}O{-}COEt + EtOMgCH(CO_2Et)_2 \rightarrow$
(IIa, b)

$$C_6H_4(CO)_2NCH(R)COCH(CO_2Et)_2 \xrightarrow[\text{dist. 2 h.}]{\text{steam}} C_6H_4(CO)_2NCH(R)COCH_2CO_2Et$$

(IIIa, b) (IVa, b)

a; R=H

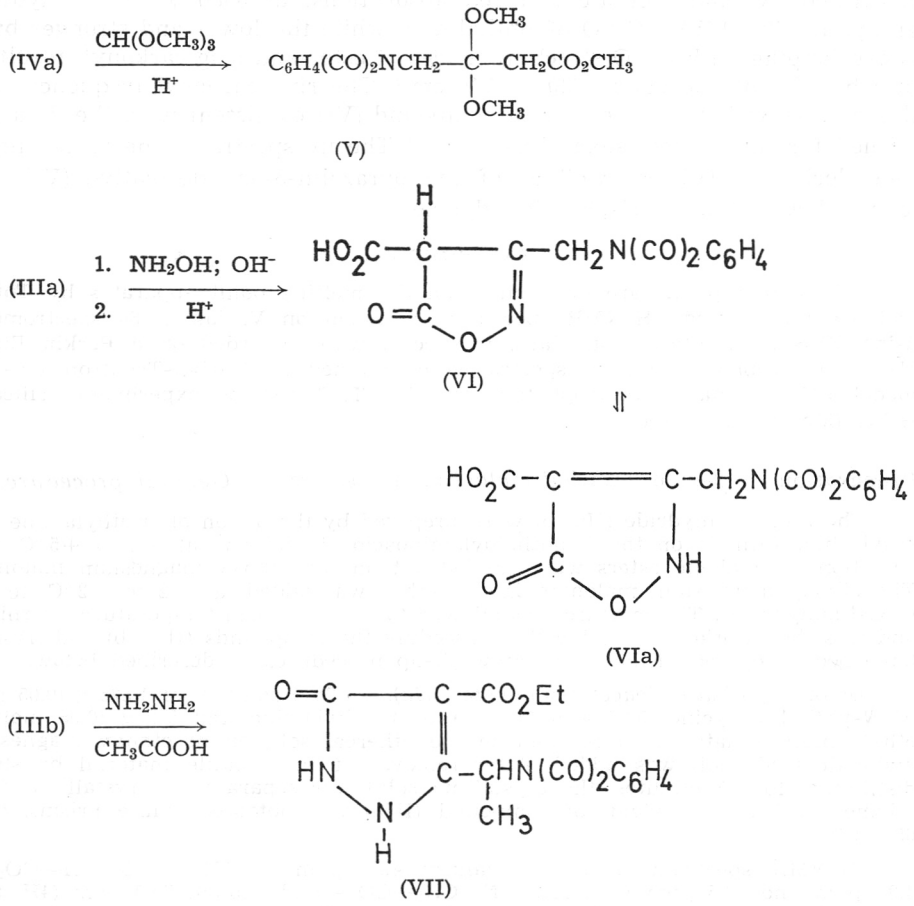
b; R=CH_3

The ketalization of ethyl (phthalimidoacetyl)acetate (IVa) with ethylene glycol is described.[11] We performed the ketalization of this compound to dimethyl ketal by Claisen's[12] method, using methyl orthoformate in absolute methanol. Beside the ketalization the transesterification occured so that the mixture of 51% of methyl (phthalimidoacetyl)acetate dimethyl ketal and 14.7% of methyl (phthalimidoacetyl)acetate was isolated. The ketal structure was supported by appearance of one singlet in the ^1H NMR spectrum at δ 3.32 ppm belonging to protons of the two methoxy groups, two singlets at 2.77 and 4.12 ppm for two isolated methylenic groups and the singlet at 3.70 ppm for methyl protons of the ester group.

Jacquier *et al.*[5] also described the synthesis of 3-hydroxiisoxazoles using β-ketoesters substituted in α-position and hydroxylamine under basic conditions followed by acidification.

We used diethyl (phthalimidoacetyl)malonate (IIIa) which is a β-ketoester substituted in the α-position with an ethoxy carbonyl group, to perform the cyclization with hydroxylamine under basic conditions which was followed by immediate acidification. As shown by TLC a mixture of two compounds was formed, one of which gave a violet colour after spraying with $FeCl_3$ reagent. By recrystallization from ethanol-water corresponding substance was isolated. It was found that during the cyclization under described conditions, the hydrolysis of ethoxycarbonyl group occured and 3-(phthalimidomethyl)isoxazolin-5-one-4-carboxylic acid (VI) was formed. Its structure was supported by appearance of two signals for unexchangeable protons of the methylene group at 4.17 ppm and of the aromatic ring at 7.83 ppm. The three signals of exchangeable protons were assigned as follows: the sligthly broadened singlet at 10.8 ppm to the proton of the carboxyl group, the singlet at 8.9 ppm, slightly

Scheme II



broadened too, to the HN< proton of isoxazolin-5-one ring, and the singlet at 3.42 ppm to the methine proton of its C_4 tautomer (VIa). The presence of following groups was confirmed by characteristic infrared absorbtions: at 3310 cm^{-1} ν NH-3210 cm^{-1} associated ν OH; 1770, 1718 ν C=O of phthalimid; 1710 ν C=O (ring); 1680 ν C=O (acid); 1610 and 1550 cm^{-1} ν C=N and ν C=C respectively.

We also performed cyclization of diethyl (α-phthalimidopropionyl)malonate (IIIb) with hydrazine hydrate in acetic acid under the stream of nitrogen. From the resulted mixture we have isolated 4-ethoxycarbonyl-3-(α-phthalimidoethyl)pyrazolin-5-one (VII). This derivate of pyrazolin-5-one was examined by TLC, and gave a purple colour after spraying with $FeCl_3$ reagent. The ^1H NMR data confirm the structure:[13] beside the signal of the four aromatic protons at 7.87 ppm and the characteristic feature of the ethyl group — triplet at 1.33 ppm and quartet at 4.33 ppm, — the spectrum shows a doublet of methyl protons at 1.80 coupled with the quartet at 6.17 ppm originated by methine proton. The broad singlet at 8.8 ppm of two exchangeable protons

is assigned to hydrazo group of the ring. The presence of following groups was confirmed by characteristic infrared absorbtions: at 3380 ν NH of hydrazo group, at 1781, 1710 ν C=O of phthalimid, while the lower and stronger band is overlapping with C=O streching modes of ester and ring carbonyl, resulting in a broad multiple band 1680 — 1740 cm^{-1}. The ring carbonyl frequency is in this case as well as in the case of compound (VI) consistent with the data published for substituted isoxazolin-5-ones.[14] The uv spectra of the isoxazolin-5--one derivative (VI), as well as of the pyrazolin-5-one derivative (VII) are identical with that of *N*-phthaloylglycine.

EXPERIMENTAL

All melting points are determined on the melting point apparatus by Tottoli and are uncorrected. ^{1}H-NMR spectra were taken on Varian T 60 spectrometer using TMS as a internal standard, ir spectra were revorded on a Perkin Elmer M-137 spectrophotometer, uv spectra were obtained on Varian-Techtron UV-VIS model 635 automatic spectrophotometer. For TLC control experiments silicagel HF_{254} (Merck) was used.

Preparation of β-keto-γ-phthalimidoaliphatic esters. — General procedure.

The mixed anhydride (IIa, b) were prepared by the action of triethylamine and ethyl chloroformate on the N-phthaloylaminoacids in toluene at +2 to +5 °C. The acylations of malonic esters were carried out on the ethoxy magnesium malonate. The ethoxy magnesium malonate in dry ether was added, at —2 to +2 °C, to the mixed anhydrides. The mixture was allowed to come to room temperature overnight, and was then worked up. Using this procedure the compounds (IIIa, b) and (IVa, b) have been prepared, using different work-up procedures as described below.

Diethyl (phthalimidoacetyl)malonate (IIIa). — To a solution of 10.25 g (0.05 mol) of *N*-phthaloylglycine, 5.05 g (0.05 mol) of triethylamine and 5.4 g (0.05 mol) of ethyl chloroformate in 50 ml toluene the ethereal solution of ethoxy magnesium malonate (0.05 mol) was added. After removal of the volatile material by steam distillation for 15 minutes, the crystalline solid was separated, recrystallized from ethanol; 6.15 g (35% yield) of compound (IIIa) was obtained, white prisms, m. p. 68—69 °C.

^{1}H-NMR spectrum ($CDCl_3$) δ values: 4.60 ppm (s, 1H, —CO—C*H*—CO_2—); 4.80 ppm and 4.95 ppm (2 s, 2H, >N—CH_2—CO— and enolic); 7.80 ppm (4H, aromatic); 14.47 ppm (s, 1H, O*H* of the enolic form). The assignment of chemical shift value for methylenic protons of the enol form at 4.95 ppm was confirmed by taking the spectrum in pyridin, which showed in addition to 1H- singlet for —OH at 14.47 ppm only one singlet for 2H of the methylene group at 4.88 ppm with no evidence for the methine proton.

Diethyl (α-phthalimidopropionyl)malonate (IIIb). — To a solution of 10.95 g (0.05 mol) of *N*-phthaloylalanine, 5.05 g (0.05 mol) of tritheylamine and 5.4 g (0.05 mol) of ethyl chloroformate in 50 ml toluene the ethereal solution ethoxy magnesium malonate (0.05 mol) was added. After removal of the volatile material by steam distillation during 15 minutes the separated residual oily product was crystallized from ethanol; 7.6 g (40% yield) of compound (IIIb) was obtained colourless plates, m. p. 73—74 °C.

H^1-NMR spectrum, ($CDCl_3$) δ values: 1.20 and 1.27 ppm (t, two overlapping, 6H, —CH_2—CH_3); 1.70 ppm (d, 3H, CH—CH_3); 4.23 ppm (q, 4H, —CH_2—CH_3); 4.67 ppm (s, —CO—C*H*—CO—); 5.17 ppm (q, 1H —C*H*—CH_3); 7.87 ppm (4H, aromatic H); 13.8 ppm (s, O*H* of the enolic form).

Ethyl (phthalimidoacetyl)acetate (IVa). — 6.15 g (0.017 mol) of diethyl (phthalimidoacetyl)malonate (IIIa) in 100 ml benzene was subjected to steam distillation for 2 h. The separated crystalline solid 4.13 g (30% yield) was recrystallized from ethanol; white needles m. p. 111 °C.

^{1}H-NMR spectrum ($CDCl_3$), δ values: 1.34 ppm (t, 3H, —CH_2—CH_3); 4.73 ppm (s, 2H, N—CH_2—CO—); 4.30 ppm (q, 2H, —CH_2—CH_3); 3.66 ppm (s, 2H, —CO—CH_2—CO—O—R); 7.80 ppm (4H, aromatic H).

Ethyl (α-phthalimidopropionyl)acetate (IVb). — 3.6 g (0.01 mol) of diethyl (α-phthalimidopropionyl)malonate (IIIb) in 50 ml benzene was subjected to steam distillation for 2 h. The separated oily product was extracted with three 20 ml portions of ether. The combined ether extracts were dried and evaporated *in vacuo*. Distillation of the residue, b. p. 80—85 °C/0,01 Torr, gave 1.1 g (39%) of compound (IVb) as colourless oil, which slowly crystallized, m. p. 43—44 °C.

^{1}H-NMR spectrum, ($CDCl_3$), δ values: 1.20 ppm (t, 3T, —CH_2—CH_3); 1.63 ppm (d, 3H, CH_3—CH—CO—); 3.53 ppm (s, 2H, —CO—CH_2—CO_2—); 4.17 ppm (q, 2H, O—CH_2—CH_3); 5.03 ppm (q, 1H, CH_3—CH—CO—); 7.7—8.1 ppm (4H, aromatic H).

Anal. $C_{15}H_{15}NO_5$ (289.278) calc'd.: C 62.28; H 5.23; N 4.84%
found: C 62.37; H 5.52; N 5.00%

Methyl (phthalimidoacetyl)acetate dimethyl ketal (V). — To a suspension of 8.25 g (0.03 mol) of ethyl (phthalimidoacetyl)acetate and of 13.35 g (13.1 ml; 0.12 mol) of methyl orthoformate in 33 ml absolute methanole, one drop of conc. H_2SO_4 was added and the mixture was left at room temperature for two days with occasional heating to 60—65 °C. Additional seven drops of conc. H_2SO_4 were successively added in course of the reaction. After removing the methyl (phthalimidoacetyl)acetate, which crystallized from the mixture (800 mg), the filtrate was diluted with 300 ml ether, washed with water to which a few drops of 25% ammonia had previously been added and dried ($MgSO_4$). After evaporation of ether under reduced pressure the crystalline solid gave 8.5 g of a mixture of two compounds. Fractional crystallization from ethyl acetate-petroleum other yielded 4.7 g (51%) white hexahedrons m.p. 92—100 °C of methyl (phthalimidoacetyl)acetate dimethyl ketal and additional 350 mg (overall yield 1.15 g; 14.7%) m. p. 137—139 °C., long white prisms of methyl (phthalimidoacetyl)acetate were isolated. The analytical sample of (V) was recrystallized from ethyl acetate petroleum ether, m. p. 118—119 °C.

^{1}H-NMR spectrum, ($CDCl_3$), δ values: 2.77 ppm (s, 2H, —CH_2—CO_2CH_3); 3.32 ppm (s, 6H, —$C(OCH_3)_2$); 3.70 ppm (s, 3H, —CO_2CH_3); 4.12 ppm (s, 2H, >N—CH_2—C—); 7.8 ppm (4H, aromatic H).

Ir (KBr): 2845, 2825 (two methoxy groups); 1779, 1718 (phthalimid), 1748 cm^{-1} (ester).

Anal. $C_{15}H_{17}NO_6$ (307.077) calc'd.: C 58.67; H 5.57; N 4.56%
found: C 58.90; H 5.51; N 4.37%

The analytical sample of methyl (phthalimidoacetyl)acetate recrystallized from ethyl acetate petroleum ether, m. p. 138—139 °C.

^{1}H-n. m. r. spectrum, ($CDCl_3$), δ values: 3.60 ppm (s, 2H, —CO—CH_2—); 3.77 ppm (s, 3H, —CO_2CH_3); 4.67 ppm (s, 2H>N—CH_2—C—); 7.8 ppm (4H, aromatic H).
Ir (KBr); 1785, 1755, 1723 and 1415 cm^{-1}.

Anal. $C_{13}H_{11}NO_5$ (261.23) calc'd.: C 59.76; H 4.24; N 5.36%
found: C 59.53; H 4.18; N 5.22;

3-(Phthalimidomethyl)isoxazolin-5-one-4-carboxylic acid (IV). — To a stirred solution of 1.39 g (0.02 mol) of hydroxylammonium chloride and 1.6 g (0.04 mol) of sodium hydroxide in 20 ml water ,a suspension of 6.95 g (0.02 mol) of diethyl (phthalimidoacetyl)malonate (IIIa) in 30 ml ethanol was edded in small portions during 30 min. at 0—5 °C. The mixture was stirred until being homogeneous and diluted with 6 ml of water. After standing at 4 °C for 1 h. the mixture was acidified to pH=2 using conc. HCl. TLC (benzene:ethyl acetate:formic acid 30:30:2) showed two spots, one of which gave a violet colour after spraying with $FeCl_3$. The crystalline precipitate was filtered off, and dried to give 1.86 g of 3-(phthalimidomethyl)isoxazolin-5-one-4-carboxylic acid (VI); pale pink needles m. p. 185—6 °C. The filtrate was extracted with three 50 ml portions of ether: petroleum ether (4:1). The combined extracts were dried ($MgSO_4$) and evaporated to oily residue which crystallized after standing. After crystallization from ethanol:water, 0.74 g m. p.

185—6 °C of (VI) was obtained; the overall yield of pure 3-(phthalimidomethyl)isoxazolin-5-one-4-carboxylic acid (VI) was 2.6 g (45%), m. p. 185—6 °C.

^{1}H-NMR spectrum, (DMSO) δ values: 3.42 ppm and 8.9 ppm (2s, 1H methine proton at C_4 of isoxazolin-5-one ring and *HN*< of the tautomeric isoxazolin-5-one ring VIa); 4.17 ppm (s, 2H, >N—CH_2—C=C); 7.83 ppm (s, 4H, aromatic H); 10.8 ppm (s, 1H —COO*H*).

Ir (KBr): 3310, 3210, 1770, 1718, 1710, 1680 and 1610 cm^{-1}.

Anal. $C_{13}H_8O_6N_2$ (288.162) calc'd.: C 54.18; H 2.77; N 9.72%
found: C 54.39; H 2.46; N 9.52%

4-Ethoxycarbonyl-3-(α-phthalimidoethyl)pyrazolin-5-one (VII). — To a mixture of 3.6 g (0.01 mol) of diethyl (α-phthalimidopropinoyl)malonate (IIIb) and 16 ml of acetic acid, 0.48 ml (0.50 g; 0.01 mol) of hydrazine hydrate was added. The resulting mixture was heated at 95—100 °C for 3 hours, under a stream of nitrogen. The reaction mixture was evaporated under reduced pressure to dryness, the residue disolved in 30 ml of CH_2Cl_2, washed with three 15 ml portions of water and dried ($MgSO_4$). After evaporating of dichloromethane, 2.5 g (75.9%) of a pale yellow oil was obtained. The TLC control (benzene:ethyl:acetate:formic acid 30:30:2) showed the crude product to be complex mixture, which after crystallization from acetone:ether:cyclohexane (2:2:1), gave colourless prisms, 1.04 g (31.6%), m. p. 178—181 °C. (TLC of the sample showed only one spot giving a purple colour after spraying with $FeCl_3$ reagent).

^{1}H-NMR spectrum ($CDCl_3$) δ values: 1.33 ppm (t, 3H, —CH_2CH_3); 1.80 ppm (d, 3H, CH_3—CH); 4.33 ppm (q, 2H, —CH_2—CH_3); 6.17 ppm (q, 1H, *H*C—CH_3); 7.87 ppm (4H, aromatic H); 8.8 ppm (broad signal, 1H + 1H, —*H*N—N*H*—).

Ir (KBr): 3380, 2600, 3000, 1780, 1710, 1615, 1570, 1510, 1385, 1330 and 1100 cm^{-1}.

Anal. $C_{16}H_{15}N_3O_5$ (329.0) calc'd.: C 58.36; H 4.56; N 12.77%
found: C 58,07; H 4.43; N 12.59%.

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SAŽETAK

Priređivanje i ciklizacija nekih β-keto-γ-ftalimido alkil estera

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Opisana je priprema (α-ftalimidoacil)malonata (IIIa, b) pomoću mješovitih anhidrida (IIa, b), te njihovo monodeetoksikarboniliranje u (α-ftalimidoacil)acetate (IVa, b). Ciklizacija dietil(ftalimidoacetil)malonata (IIIa) s hidroksilaminom dala je 3-(ftalimidometil)izoksazolin-5-on-4-karboksilna kiselinu (VI), dok je malonski derivat (IIIb) reakcijom s hidrazinom dao 4-etoksikarbonil-3-(α-ftalimidoetil)pirazolin-5-on (VII). Spoj (IVa) djelovanjem metilortoformijata u apsolutnom metanolu dao je metil(ftalimidoacetil)acetat-dimetil-ketal (V). Strukture opisanih spojeva razmatrane su na osnovi podataka dobivenih iz spektara ^{1}H-nuklearne magnetske rezonancije, kao i infracrvenih spektara.

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