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SYNTHESIS OF ALIPHATIC α-DIOXIMES FROM OXAZOLE DERIVATIVES

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Previously it was established that the reaction of 2,4-diphenyl-5-aryloxazoles with Br_2 in aqueous AcOH in the presence of AcONa with boiling leads to cleavage of the oxazole ring and formation of arylphenylglyoxal [1]. However, the severe conditions prevent the use of this method for preparation of unstable aliphatic α-diketones from 4,5-dialkyloxazoles.

For the synthesis of aliphatic α-dicarbonyl compounds, in the present paper we studied the halogenation of oxazole derivatives (Ia, b) and (XII a-c) under milder conditions. Oxazoles (Ia, b) can be considered as internal enol ethers, which are obtained by cyclodehydration of N-acyl-α-amino ketones (IIa, b) [2]. The double bond of the enol ethers can undergo addition with N-bromosuccinimide (NBS) [3, 4]. Therefore, it seemed of interest to study the reaction of (Ia, b) with this reagent and the hydrolysis of intermediate products of the addition of (IIIa, b) to diacetyl (IV). However, contrary to expectations, the bromination of (Ib), even with excess NBS in CCl_4, occurs only at methyl groups without involvement of the oxazole ring. The structure of the resulting 2-phenyl-4,5-bis(bromomethyl)oxazole (V) was proven by elemental analysis, the proton NMR spectrum (see the Experimental part), and conversion to 2-phenyl-4,5-bis(acetylthiomethyl)- and 2-phenyl-4,5-bis(phenylacetoxymethyl)oxazoles (VI) and (VII) in the presence of AcSNa and $PhCH_2COOAg$

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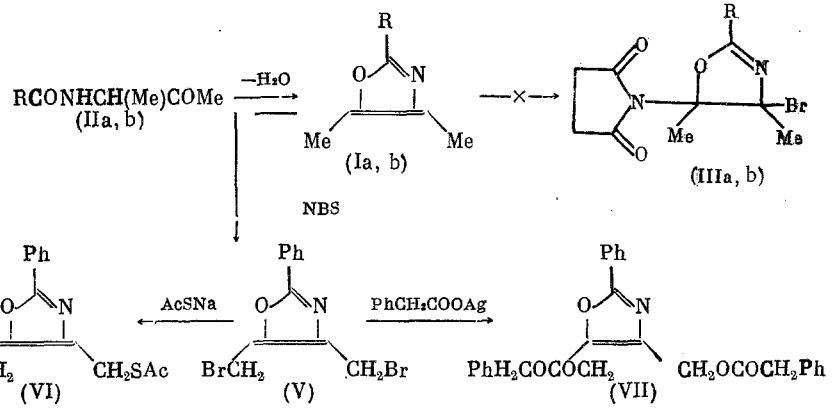
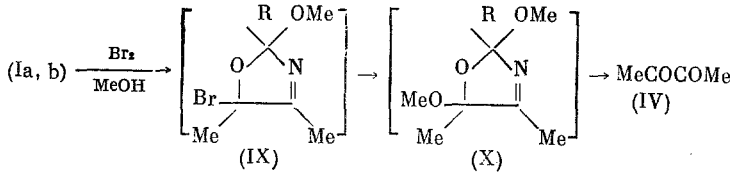


R = Me (Ia), (IIa), (IIIa); Ph(Ib), (IIb), (IIIb).

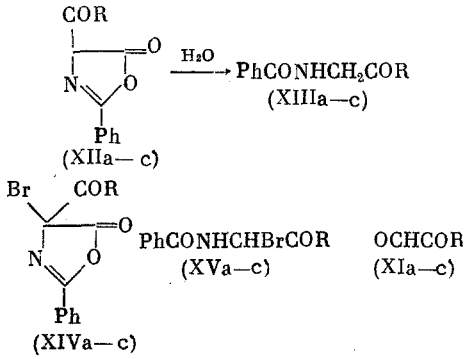
Cleavage of the oxazole ring (Ia, b) could be achieved in the presence of Br_2 in MeOH at 20°C with subsequent treatment of the reaction mixture with water. In this case, (IV) was formed, isolated as dimethylglyoxime (VIII) with total yields of 45 and 88%.

In accordance with the familiar concepts of the mechanism of bromination of 2-methyl-5-phenyloxazole in MeOH [5], the conversion of (Ia, b) to (IV) can be represented as a multistep process including the intermediate formation of bromomethoxy and dimethoxy derivatives (IX) and (X) and subsequent hydrolytic cleavage of (X) to (IV)



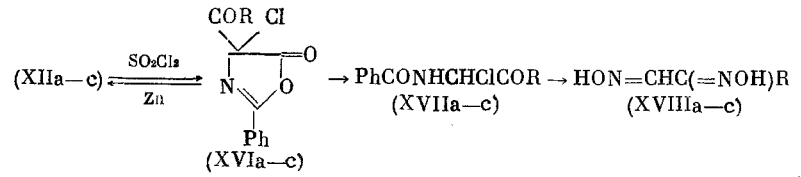
Analogous conversion of 2-phenyl-5-methyloxazole [2] to methylglyoxal (XIa) could not be carried out.

Therefore, for the synthesis of (XIa) and other α-keto aldehydes, we chose as the starting substances oxazole derivatives (XIIa-c), capable of facile hydrolytic cleavage to 1-benzamido-2-alkanones (XIIIa-c) [6, 7]. It could be assumed that bromination of (XIIa-c) at C^4 and subsequent cleavage of intermediate bromides (XIVa-c) like (XIIa-c) would lead to 1-bromo-1-benzamido ketones (XVa-c) or α-keto aldehydes (XIa-c). For this purpose, we studied the reactions of (XIIa-c) with Br_2 and NBS in different solvents (MeOH, AcOH, conc. HCl, and CH_2Cl_2) at 20°C. However, after hydrolysis of the bromination products with water or hydrochloric acid, in no case were (XVa-c) or (XIa-c) observed in the reaction mixtures.



R = Me (XIIa), Et (XIIb), Pr (XIIc).

Favorable results were achieved in going to the corresponding chlorides (XVIa-c), which were obtained by the reaction of (XIIa-c) with SO_2Cl_2 in CH_2Cl_2



The structure of (XVIa-c) was confirmed by proton NMR spectra and reduction of (XVIa) by Zn in AcOH to the starting (XIIa). Hydrolytic cleavage of (XVIa-c) with a mixture of AcOH and HCl and subsequent treatment of the intermediate 1-chloro-1-benzamido ketones (XVIIa-c) [7] with hydroxylamine afforded dioximes of α-keto aldehydes (XVIIIa-c) in 50% yield based on (XIIa-c).

The obtained α-dioximes (VIII) and (XVIIIa-c) can be hydrolyzed to free α-dicarbonyl compounds or used as their precursors in situ [7, 8].

EXPERIMENTAL

The UV spectra were recorded in alcohol on a Specord UV-VIS instrument, the IR spectra were recorded in a tablet with KBr on a UR-20 instrument, and the proton NMR spectra were recorded on a DA-60 IL instrument (HMDS internal standard). Thin-layer chromatography was carried out on UF-254 Silufol (observation of spots in UV light).

2-Phenyl-4,5-dimethyloxazole (Ib). A mixture of 6 ml of conc. H_2SO_4 and 10 ml of Ac_2O was added gradually to a solution of 6 g of 3-benzamido-2-butanone [9] in 8 ml of Ac_2O with cooling with solid CO_2 and stirring. The reaction mixture was heated for 1 h on a boiling water bath, then poured into an excess of a solution of NaOH with ice, and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and evaporated, and the residue was distilled in vacuo. Obtained: 4.3 g (79%) of (Ib), bp 109-110°C (2 mm), mp 47-48°C, R_f 0.63 (AcOEt). Proton NMR spectrum (CCl_4, δ, ppm): 1.96 s (Me), 2.08 s (Me), 7.12-7.42 (meta and para protons of the aromatic ring), 7.80-8.04 (ortho protons of the aromatic ring). Found: C 75.95; H 6.54; N 8.24%. $C_{11}H_{11}NO$. Calculated: C 76.27; H 6.40; N 8.09%.

2-Phenyl-4,5-bis(bromomethyl)oxazole (V). A mixture of 1 g of 2-phenyl-4,5-dimethyloxazole (Ib) and 2.36 g of NBS in 10 ml of CCl_4 was boiled for 1 h, the succinimide precipitate was filtered, the mother liquor was evaporated in vacuo, and 1.7 g (89%) of (V) was obtained, mp 128-130°C (after washing with MeCN and recrystallization from CCl_4), R_f 0.72 (AcOEt–benzene, 1:4). Proton NMR spectrum (CCl_4, δ, ppm): 4.30 s (CH_2Br), 4.48 s (CH_2Br), 7.23-7.50 (meta and para protons of the aromatic ring), 7.83-8.11 (ortho protons of the aromatic ring). Found: C 39.88; H 2.99; N 4.29; Br 48.63%. $C_{11}H_9Br_2NO$. Calculated: C 39.97; H 2.74; N 4.23; Br 48.28%.

2-Phenyl-4,5-bis(acetylthiomethyl)oxazole (VI). A solution of AcSK (from 1.1 ml of AcSH and 0.59 g of KOH in 3 ml of H_2O) was added gradually to a solution of 1.7 g of (V) in 15 ml of acetone with stirring, and the whole was kept at 20°C for 3 h. The precipitate was filtered, washed with water and with acetone, and dried in air. We obtained 0.67 g of (VI). The mother liquor was evaporated in vacuo, and the residue was treated with water and $NaHCO_3$ to pH 7 and extracted with AcOEt. The extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was crystallized from acetone at –70°C. An additional 0.31 g of (VI) was obtained, and its total yield was 0.98 g (53%), mp 105-106°C (from alcohol), R_f 0.36 (AcOEt–benzene, 1:5). Proton NMR spectrum (CCl_4, δ, ppm): 2.30 s (COMe), 2.34 s (COMe), 4.04 s (CH_2S), 4.30 s (CH_2S), 7.32-7.48 (meta and para protons of the aromatic ring), 7.88-8.08 (ortho protons of the aromatic ring). Found: C 56.34; H 4.84; N 4.48; S 20.04%. $C_{15}H_{15}O_3NS_2$. Calculated: C 56.06; H 4.70; N 4.35; S 19.96%.

2-Phenyl-4,5-bis(phenylacetoxymethyl)oxazole (VII). A mixture of 0.85 g of (V) and 1.62 g of Ag phenylacetate in 12 ml of MeCN was stirred for 12 h at 20°C, the filtrate was evaporated in vacuo, and the residue was chromatographed on SiO_2 (160/100 mesh). With a benzene–AcOEt mixture (1:4), 0.99 g (77%) of (VII) was eluted, mp 64-65°C (after low-temperature crystallization from ether), R_f 0.65 (benzene–AcOEt, 5:1). Proton NMR spectrum (CCl_4, δ, ppm): 3.42 s (2 CH_2Ph), 4.94 s (CH_2), 5.05 s (CH_2), 7.06 s (2 CH_2Ph), 7.16-7.41 (meta and para protons of the aromatic ring), 7.78-8.03 (ortho protons of the aromatic ring). Found: C 73.56; H 5.31; N 3.43%. $C_{27}H_{23}NO_5$. Calculated: C 73.53; H 5.25; N 3.14%.

Dimethylglyoxime (VIII). To a solution of 0.5 g of (Ib) in 5 ml of methanol was added 0.16 ml of Br_2 with stirring, the whole was kept at 20°C for 1 h, and 5 ml of H_2O was added. The mixture was kept at 20°C for 12 h and heated at 90°C for 1.5 h, and a solution of diacetyl (IV) was obtained, R_f 0.66 (AcOEt—benzene, 1:1, development of the spot with a solution of 2,4-dinitrophenylhydrazine). A reference sample of (IV) had the same value of R_f. To a solution of (IV) were added 2 g of $HCl \cdot H_2NOH$ and 1.16 g of KOH in 5 ml of H_2O, the whole was heated for 1.5 h at 90-100°C and cooled to 20°C, and the precipitate was filtered, washed with an aqueous solution of $NaHCO_3$ and with water, and dried in air. We obtained 0.24 g of (VIII). The filtrate was treated with excess $Ni(OAc)_2$ and the red precipitate was filtered and washed with water and ether. We obtained 0.07 g of a Ni complex of (VIII). The total yield of (VIII) was 0.3 g (88%), mp 238-240°, R_f 0.81, ether, and development of the spot with a solution of $Ni(OAc)_2$. UV spectrum (alcohol): λ_{max}, 230 nm. Proton NMR spectrum (C_5D_5N, δ, ppm): 2.31 s (2Me), 5.03 s (2OH). A reference sample of (VIII) had the same characteristics [10]. We obtained 0.15 g (45%) of (VIII) similarly from 0.3 g of 2,4,5-trimethyloxazole (Ia) [11].

2-Phenyl-4-chloro-4-acetyl-5-oxazolinone (XVIa). To a solution of 0.5 g of 2-phenyl-4-acetyl-5-oxazolinone (XIIa) [6] in 2 ml of CH_2Cl_2, 0.24 ml of SO_2Cl_2 was added with stirring, and the whole was kept at 20°C for 1 h and evaporated in vacuo. We obtained 0.54 g (93%) of oily (XVIa), R_f 0.49 (acetone). IR spectrum (ν, cm^{-1}): 1730 (COMe), 1850 (C=O of the ring). Proton NMR spectrum (CCl_4, δ, ppm): 2.10 s (Me), 7.30-7.76 (meta and para protons of the aromatic ring), 7.86-8.13 (ortho protons of the aromatic ring).

To a solution of 0.4 g of (XVIa) in 7 ml of AcOH, 0.5 g of Zn powder was added gradually with stirring, and after heating ceased, the excess Zn was filtered, and the mother liquor was diluted with water. The precipitate was filtered, washed with water, and dried in air. We obtained 0.24 g (70%) of (XVIa), mp 194-195°C (from AcOEt) [6].

To 0.54 g of (XVIa) in 3 ml of conc. HCl, AcOH was added dropwise until complete dissolution of (XVIa), and the whole was kept at 20°C for 2 h, then diluted with H_2O, and extracted repeatedly with benzene. The extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was crystallized from ether at −70°C. We obtained 0.09 g (25%) of 1-chloro-1-benzamidoacetone (XVIIa), mp 56°C, R_f 0.53 (AcOEt). The obtained (XVIIa) did not give a melting-point depression with a reference sample [7] and had an R_f value identical to it.

Nickel Complex of Methylglyoxime (XVIIIa). A mixture of 0.54 g of (XVIa), 3 ml of conc. HCl, and 3 ml of AcOH was kept at 20°C for 2 h. The obtained solution of (XVIIa) was diluted with 10 ml of water, $NaHCO_3$ was added to pH 7, 1.02 g of $HCl \cdot H_2NOH$ was added, the pH was again brought to 7, and the whole was heated at 100°C for 4 h, with pH 7 being maintained by periodic addition of $NaHCO_3$. The solution was cooled to 20°C and treated with excess $Ni(OAc)_2$. The resulting red precipitate was filtered, washed with water and with ether, and dried in air. We obtained 0.15 g (47%) of the Ni complex of (XVIIIa), R_f* 0.66 (ether). UV spectrum: λ_{max} 263 nm, IR spectrum (ν, cm^{-1}): 740, 1259, 1570, 2920, 3050, 3410-3470. A reference sample of the Ni complex of (XVIIIa) [10] had the same characteristics.

Nickel Complex of Ethylglyoxime (XVIIIb). Similarly, from 0.5 g of 2-phenyl-4-propionyl-5-oxazolinone (XIIb) [6] and 0.225 ml of SO_2Cl_2, we obtained 0.55 g (95%) of 2-phenyl-4-chloro-4-propionyl-5-oxazolinone (XVIb), oil, R_f 0.58 (acetone). IR spectrum (in a thin layer, ν, cm^{-1}): 1735 ($COCH_2$), 1850 (C=O of the ring). Proton NMR spectrum (CCl_4, δ, ppm): 1.05 t (Me, J = 8 Hz), 2.95 q $COCH_2$, J = 8 Hz), 7.30-7.65 (meta and para protons of the aromatic ring), 7.81-8.13 (ortho protons of the aromatic ring).

With hydrolytic cleavage of 0.55 g of (XVIb) and subsequent oximation as described above, we obtained 0.16 g (49%) of the Ni complex of (XVIIIb), R_f 0.28 (AcOEt—benzene, 1:4). UV spectrum: λ_{max}, 263 nm. IR spectrum (ν, cm^{-1}): 735, 1245, 1558, 2946, 2980, 3350-3460. A reference sample of the Ni complex of (XVIIIb) [10] had the same characteristics.

2-Phenyl-4-butyryl-5-oxazolinone (XIIc). This compound was obtained from hippuric acid and butyric anhydride according to [6], mp 172-173°C (from AcOEt), R_f 0.53 (AcOEt—benzene, 1:1). IR spectrum (ν, cm^{-1}): 1770-1775 (C=O of the ring). Proton NMR spectrum (C_5D_5N, δ, ppm): 1.00 t (Me, J = 7 Hz), 1.88 m (CH_2), 3.13 t (=C(OH)$\underline{CH_2}$, J = 7 Hz), 7.25-7.50 (meta and para protons of the aromatic ring), 7.75-8.13 (ortho protons of the aromatic ring).

*The R_f value of the Ni complexes of (XVIIIa-c) was determined after their treatment with conc. HCl, and the spots were developed with a solution of $Ni(OAc)_2$.

Nickel Complex of Propylglyoxime (XVIIIc). By the reaction of 0.17 ml of SO_2Cl_2 with 0.4 g of (XIIc) in 3 ml of CH_2Cl_2, we obtained 0.41 g (89%) of 2-phenyl-4-chloro-4-butyryl-5-oxazolinone (XVIc), oil, R_f 0.69 (acetone). IR spectrum (in a thin layer, ν, cm^{-1}): 1725 ($COCH_2$), 1850 (C=O of the ring). Proton NMR spectrum ($CDCl_3$, δ, ppm): 0.96 t (Me, J = 7 Hz), 1.70 m (CH_2), 2.96 t ($COCH_2$, J = 7 Hz), 7.32-7.72 (meta and para protons of the aromatic ring), 7.91-8.18 (ortho protons of the aromatic ring).

From 0.41 g of (XVIc), as described above, we obtained 0.15 g (55%) of the Ni complex of (XVIIIc), R_f 0.66 (AcOEt–benzene, 1:1), UV spectrum: λ_{max} 263 nm.

Propylglyoxime (XVIIIc). A mixture of 0.2 g of the Ni complex of (XVIIIc) and 1 ml of dilute HCl (1:3) was stirred for 5 min at 20°C and then extracted with ether. The extract was dried with $MgSO_4$ and evaporated in vacuo, and 0.13 g (79%) of (XVIIIc) was obtained, mp 122-124°C (after washing with benzene), R_f 0.66 (AcOEt–benzene, 1:1). The obtained (XVIIIc) did not give a melting-point depression with a reference sample [7] and had an R_f value identical to it.

CONCLUSIONS

1. Dimethylglyoxime was obtained by bromination of 2,4,5-trimethyl- or 2-phenyl-4,5-dimethyloxazoles in methanol and subsequent oximation.

2. Chlorination of 2-phenyl-4-acyl-5-oxazolinones with sulfuryl chloride, hydrolytic cleavage of the resulting 4-chloro derivatives, and subsequent oximation of the intermediate 1-chloro-1-benzamido-2-alkanones afforded dioximes of α-keto aldehydes.

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