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Reactions of *N*-Acetyl- and *N*-Ethoxycarbonyl-2-(1-cycloalken-1-yl)anilines with *meta*-Cloroperbenzoic Acid

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Abstract—Reaction of *N*-ethoxycarbonyl-2-(1-cycloalken-1-yl)anilines with *meta*-cloroperbenzoic acid leads to the corresponding 2-[1-*o*-(3-chlorobenzoyl)-2-hydroxycyclopent-1-yl]anilines. 5-(2-Acetylaminophenyl)-5-oxopentanic or 6-oxohexanic acids are formed as main products in the reaction of *N*-acetyl-2-(1-cycloalken-1-yl)anilines with *m*-chloroperbenzoic acid in CH_2Cl_2. *N*-Acetyl-2-(1-cyclopenten-1-yl)-3,6-dimethylaniline is an exception in this series since its reaction stops at the stage of epoxide formation.

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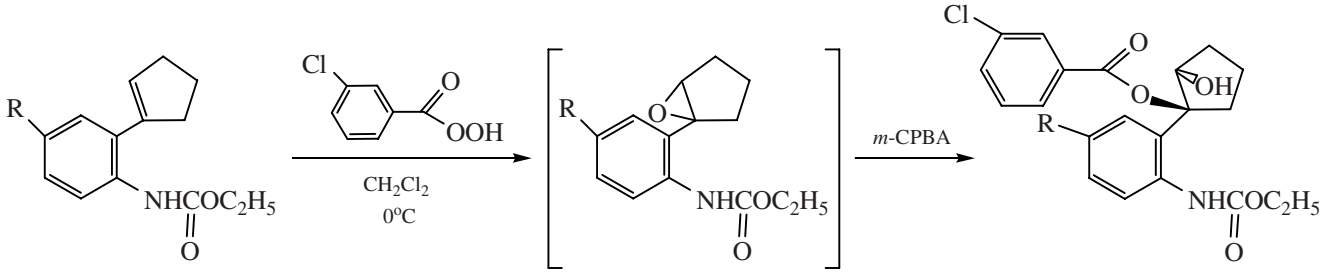
Aniline 2-cycloalkenyl derivatives are used in the synthesis of natural compounds [1], show good inhibiting properties of steel in aggressive media [2] and possess local anesthetic activity like well-known anesthetics [3, 4].

In this report we outline results of our investigation of the reaction of 2-(1-cycloalken-1-yl)anilines with *m*-chloroperbenzoic acid.

Reactions of *N*-ethoxycarbonyl-2-(1-cycloalken-1-yl)anilines **Ia, Ib** with *m*-chloroperbenzoic acid afford esters **IIa, IIb** in high yields. It is evident that the esters are the products of secondary reaction of intermediate epoxide cleavage according to A.K. Krasusky's rule (Scheme 1). Epoxide **A** was not found in the reaction mixture.

Protective group at the nitrogen atom affects the structure of the reaction products. A mixture of benzoxazine **IVa–IVd** and ketoacid **Va–Vd**, where the latter was the main reaction product was obtained from *N*-acetyl derivatives **IIIa–IIIc** under analogous conditions. In the reaction mixture ester **VIb** was found in the case of anilide **IIIb**. Formation of compounds **IV–VI** we ascribe to further transformations of intermediate epoxide **A**. The intramolecular cyclization of the epoxide gave benzoxazines **IVa-IVd**, and the reaction with *m*-chloroperbenzoic acid furnished ester **VIb**. The known intramolecular rearrangements of epoxide **B** [5,6] gave rise to ketone **B**, which underwent subsequent oxidation into ketoacid **Va–Vd** (Scheme 2).

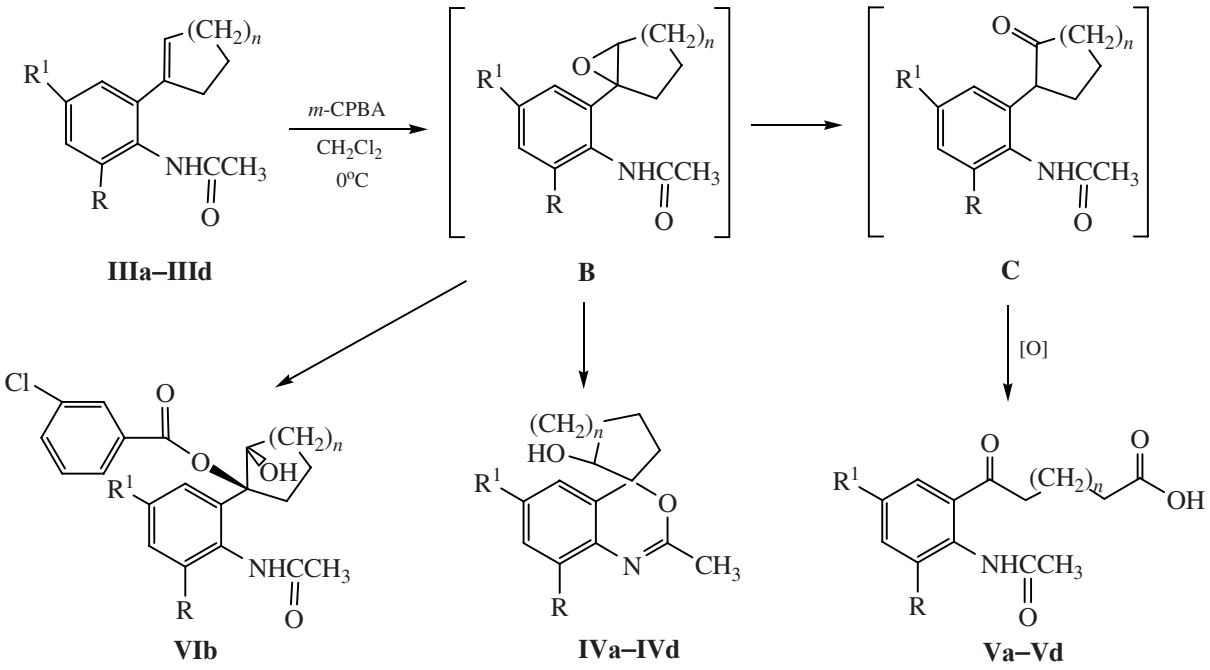
Scheme 1.



Ia, Ib **A** **IIa, IIb**

R = H (**a**), Me (**b**).

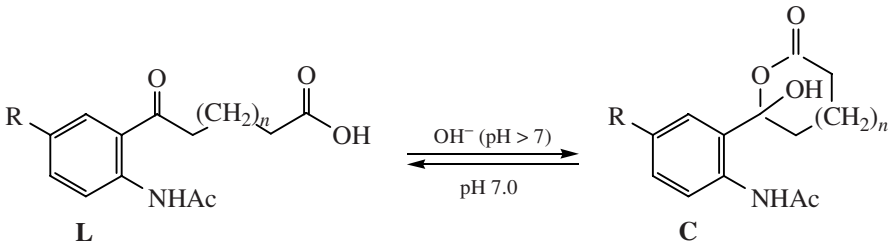
Scheme 2.



n = 1: R = R' = H (**a**); R = H, R' = Me (**b**); R = Me, R' = H (**c**); *n* = 2: R = H, R' = Me (**d**).

Ketoacid did not pass into the aqueous solution and did not form potassium or sodium salts at the treatment with aqueous solution of sodium carbonate or hydrogen carbonate evidently due to the transformation of the linear form **L** into the cyclic form **C** in alkaline medium. The equilibrium is displaced to the linear form in neutral solutions (Scheme 3).

Scheme 3.

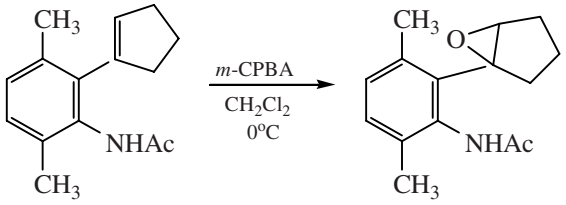


We observed in deutrochloroform only signals of ketoacid **L** since a base was absent.

Reaction of *N*-acetyl derivative **IIIe** with *m*-chloroperbenzoic acid stopped at the stage of epoxide **VII** formation. In this case obviously the presence of methyl group at C^3-position of aromatic ring created certain steric hindrances for the formation of esters of type **VIa** or benzoxazine structure of type **IVa–IVd**. The absence of the latter in the reaction mixture is caused evidently by a hindered spatial arrangement of the epoxidized cyclopentane ring that is not favorable for intramolecular S_N2-attack (Scheme 4).

The presence of the methyl substituent provided evidently a stabilizing effect on the epoxy group therefore rearrangement into ketone of type **B,** the ketoacid precursor, did not occur. Spectral analysis of compounds **II** showed that in H^1 NMR spectrum of **II** all proton signals of aromatic rings are sufficiently resolved and correspond to calculated values. In the aromatic region of the spectrum except for vicinal

Scheme 4.



IIIe **VII**

constants (7–8 Hz), a majority of signals have spin-spin coupling constants (0.5–1.5 Hz) owing to the presence of chlorine atom in the molecule. The signal of $H^{2'}$ proton of cyclopentane ring is a triplet with spin-spin coupling constant of 7.3 Hz, showing that dihedral angles with both H^3_a and H^3_b protons of methylene group C^3H_2 are approximately equal. Signals of protons from NH and OH groups are observed at δ 8.78 ppm and 2.72 ppm respectively. The ethoxy group gives rise to a triplet signal of CH_3 group and a quadruplet two-proton signal of CH_2 group.

Composition and structure of the other compounds obtained are also proved by elemental analysis and spectral methods. Characteristics of compounds **Ia–Ic** and **Va–Vc** correspond to the described ones.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at operating frequencies of 300.13 and 75.45 MHz, internal reference TMS. Elemental analysis was performed on an Analyzer M-185B. Column chromatography was carried out on a silica gel 40/70 μm (Lancaster). For TLC qualitative analysis silufol plates Sorbfil (Sorbpolymer, Stavropol') were used, detection by UV-irradiation (λ 254 nm) and iodine vapor. The mass spectra were obtained on a spectrometer MKh 1320 (70 eV).

Oxidation of *N*-acetyl- and *N*-ethoxycabonyl-2-(1-cycloalken-1-yl)anilines Ia and Ib, IIIa–IIIe with *m*-chloroperbenzoic acid. To a solution of 2 mmol of anilide **Ia**, **Ib** or **IIIa–IIIe** in 10 ml of CH_2Cl_2 was added 0.69 g of *m*-chloroperbenzoic acid in 10 ml of CH_2Cl_2, and then 0.1 g of K_2CO_3. The reaction mixture was stirred at room temperature. The reaction progress was followed by TLC, eluent benzene. Then the reaction mixture was treated by a saturated solution of $NaHCO_3$ (2×10 ml) and water (2×10 ml). The reaction products were isolated by column chromatography on silica gel, elution with benzene and benzene–ethyl acetate mixture (ratio from 9:1 to 1:1).

***N*-Ethoxycarbonyl-2-[1-*O*-(3-chlorobenzoyl)-2-hydroxycyclopent-1-yl]aniline (IIa).** A viscous transparent substance; yield 0.4 g (50%), R_f 0.3 ($CHCl_3$). ^1H NMR spectrum, $CDCl_3$, δ, ppm: 1.32 d. t (3H, CH_3, J_1 0.5, J_2 7.1 Hz), 1.40–2.55 m (6H, $3CH_2$), 2.72 b. s (1H, OH), 4.21 d. q (2H, CH_2, J_1 0.8, J_2 7.1 Hz), 5.95 t (1H, H^2, J 7.3 Hz), 6.99 d. t (1H, ArH, J_1 0.5, J_2 7.4 Hz), 7.12 d. d (1H, ArH, $J_1$1.2, J_2 7.9 Hz), 7.35–7.42 m (2H, ArH), 7.56 d. d. d (1H, ArH, J_1 1.1, J_2 2.1, J_3 7.9 Hz), 7.89 d. d. d (1H, ArH, J_1 1.0, J_2 1.5, J_3 7.9 Hz), 7.98 d. d (1H, ArH, J_1 1.0, J_2 1.8 Hz), 8.08 d (1H, ArH, J 8.0 Hz), 8.78 b. s (1H, NH). Found, %: C 62.35; H 5.25; Cl 8.86; N 3.52. $C_{21}H_{22}ClNO_5$. Calculated, %: C 62.46; H 5.49; Cl 8.78; N 3.47.

***N*-Ethoxycarbonyl-2-[1-*O*-(3-chlorobenzoyl)-2-hydroxy(cyclopent-1-yl)]-4-methylanili-ne (IIb).** A viscous transparent substance; yield 0.4 g (48%); R_f 0.3 ($CHCl_3$). ^1H NMR spectrum, $CDCl_3$, δ, ppm: 1.30 t (3H, CH_3, J 7.1 Hz), 1.41–2.54 m (6H, $3CH_2$), 2.11 s (3H, CH_3), 2.77 b. s (1H, OH), 4.20 q (2H, CH_2, J 7.1 Hz), 5.90 t (1H, H^2, J 7.3 Hz), 6.68 d (1H, ArH, J 7.2 Hz), 6.72 s (1H, ArH), 6.89 d (1H, ArH, J 7.2 Hz), 7.37 m (1H, ArH), 7.52 d. d. d (1H, ArH, J_1 1.0, J_2 2.0, J_3 7.8 Hz), 7.88 d. d. d (1H, ArH, J_1 1.0, J_2 1.5, J_3 7.8 Hz), 8.00 d. d (1H, ArH, J_1 1.0, J_2 1.7 Hz), 8.80 b. s (1H, NH). Found, %: C 64.46; H 5.89; Cl 8.72; N 3.28. $C_{21}H_{24}ClNO_5$ Calculated, %: C 63.23; H 5.79; Cl 8.48; N 3.35.

2'-Hydroxy-2-methylspiro[4*H*-benz-1-oxazine-6,1'-cyclopentane] (IVa). Yield 0.039 g (9%). Physicochemical constants correspond to [7].

2'-Hydroxy-2,6-dimethylspiro[4*H*-benz-1-oxazine-6,1'-cyclopentane] (IVb). Yield 0.05 g (11%). Physicochemical constants correspond to [8].

2'-Hydroxy-2,8-dimethylspiro[4*H*-benz-1-oxazine-6,1'-cyclopentane] (IVc). Yield 0.037 g (8%). Physicochemical constants correspond to [7].

We failed to isolate compound **IVd** in pure form.

5-(2-Acetamidophenyl)-5-oxopentanic acid (Va). Yield 0.3 g (61%). Physicochemical constants correspond to [10].

5-(2-Acetamido-5-methylphenyl)-5-oxopentanic acid (Vb). Yield: 0.247 g (47%). An amorphous powder; yield 0.247 g (47%); R_f 0.3 (benzene). ^1H NMR spectrum, $CDCl_3$, δ, ppm: 2.10 t (2H, CH_2, J 7.1 Hz), 2.14 s, 2.25 s (3H, $2CH_3$), 2.52 d. t (2H, CH_2, J_1 1.0, J_2 7.1 Hz), 3.02 t (2H, CH_2, J 7.1 Hz), 6.95 d (1H, ArH, J 8.6 Hz), 7.60 s (1H, ArH), 8.50 d (1H, H,

J 8.6 Hz), 9.75 s (1H, NH), 11.45 s (1H, COOH). Found, %: C 63.63; H 6.39; N 5.21. $C_{14}H_{17}NO_4$. Calculated, %: C 63.87; H 6.51; N 5.32.

5-(2-Acetamido-3-methylphenyl)-5-oxopentanic acid (Vc). Yield 0.33 g (63%); R_f 0.2 ($CHCl_3$–MeOH 4 : 1). Physicochemical constants correspond to [9].

5-(2-Acetamido-3-methylphenyl)-6-oxohexanic acid (Vd). A viscous transparent substance; yield 0.2 g (35%); R_f 0.3 (benzene). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 1.40-1.19 m (4H, $2CH_2$), 2.15 s, 2.20 s (3H, $2CH_3$), 2.55 t (2H, CH_2 *J* 6.6 Hz), 3.03 t (2H, CH_2, *J* 6.6 Hz), 7.20 t (1H, ArH, *J* 7.5 Hz), 7.45 d (1H, ArH, *J* 7.5 Hz), 7.60 d (1H, ArH, 7.5 Hz), 9.25 b. s (1H, NH), 9.80 s (1H, COOH). Found, %: C 63.89; H 6.35; N 5.27. $C_{15}H_{19}NO_4$. Calculated, %: C 64.11; H 6.15; N 5.34.

***N*-Acetyl-2-[1-*O*-(3-chlorobenzoyl)-2-hydroxycyclopent-1-yl]-4-methylaniline (VIb).** A viscous transparent substance; yield 0.15 g (19%); R_f 0.3 ($CHCl_3$). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 1.45–2.52 m (6H, $3CH_2$), 1.93 s (3H, CH_3), 2.70 b. s (1H, OH), 5.93 t (1H, $H^{2'}$, *J* 7.2 Hz), 6.79 d (1H, ArH, *J* 7.5 Hz), 6.83 s (1H, ArH), 7.43 m (1H, ArH), 7.54 d. d.d (1H, ArH, J_1 1.0, J_2 2.0, J_3 7.7 Hz), 7.83 d.d.d (1H, ArH, J_1 1.0, J_2 1.3, J_3 7.9 Hz), 8.06 d. d (1H, ArH, J_1 1.0, J_2 1.6 Hz), 8.60 b. s (1H, NH). Found, %: C 63.57, H 5.25; Cl 8.25; N 3.30. $C_{21}H_{21}ClNO_4$. Calculated, %: C 62.46; H 5.49; Cl 8.78; N 3.47.

***N*-Acetyl-2-(1,2-epoxycyclopent-1-yl)-3,6-dimethylaniline (VII).** A viscous transparent substance; yield 0.2 g (41%); R_f 0.5 (benzene). ^{1}H NMR spectrum, $CDCl_3$, δ, ppm: 1.42–2.39 m (6H, $3CH_2$), 2.14 s, 2.16 s, 2.19 s (3H, $3CH_3$), 3.53 s (1H, $H^{2`}$), 6.91 d (1H, ArH, *J* 7.8 Hz), 7.05 d (1H, ArH, *J* 7.8 Hz), 7.64 b. s (1H, NH). Mass-spectrum, *m/e*: 246 $[MH]^+$, 244 $[M - H]^-$. Found, %: C 73.21; H 7.59; N 5.47. $C_{15}H_{19}NO_2$. Calculated, %: C 73.44; H 7.81; N 5.71.

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