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Synthesis of Aryloxyacetaldehydes and *N*-(Aryloxyethyl)cyclohexanamine Hydrochloroides

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Abstract—Oxidation of 2-(aryloxymethyl)oxiranes with periodic acid gave a series of aryloxyacetaldehydes which reacted with cyclohexylamine in THF, and subsequent reduction of Schiff bases thus obtained with sodium tetrahydridoborate resulted in the formation of the corresponding secondary amines which were isolated and characterized as hydrochlorides.

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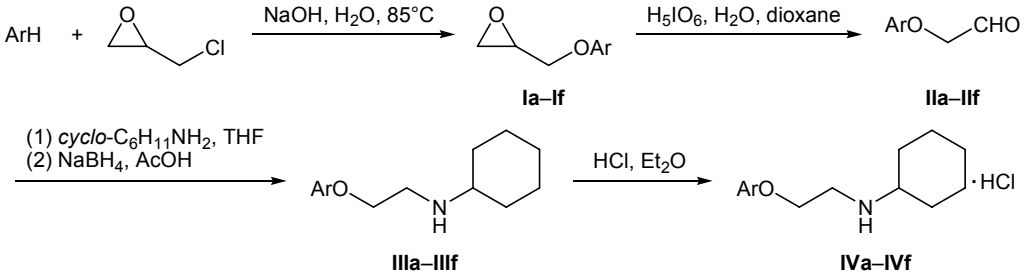
Aryloxyethanamines are known to exhibit biological activity. In particular, compounds acting as local anesthetics, adrenergic neuron blocking agents [1, 2], and dopamine D_2-receptor inhibitors [3] were found among aryloxyethanamine derivatives. These compounds are commonly synthesized by alkylation of phenols with 2-halo amines [1, 4] or of amines with 2-aryloxyethyl halides [4]. Also, reductive amination of aryloxyacetaldehydes with the use of sodium tetrahydridoborate [2, 3, 5] or hydrogen over Pd/C [6] was reported. However, the yields are not high, and they rarely exceed 50%. For example, Sakurai et al. [3] described the reaction of substituted phenoxyacetaldehydes with primary and secondary amine hydrochlorides in methanol in the presence of triethylamine, followed by reduction with $NaBH_4$, which afforded 11–31% of the corresponding 2-phenoxyethanamines.

Aryloxyacetaldehydes necessary for the synthesis of aryloxyethanamines according to [3] can also be prepared in several ways: by catalytic oxidation of 2-phenoxyethanol [7], by alkylation of phenols with bromoacetaldehyde acetals and subsequent hydrolysis [2, 8], by ozonolysis of allyl phenyl ethers [9], and by oxidation of glycerol monophenyl ether with lead tetraacetate [10]. The most appropriate procedure seems to be oxidation of 2-(aryloxymethyl)oxiranes with periodic acid in aqueous medium or aqueous dioxane, which was proposed in [11] for the synthesis of phenoxyacetaldehyde.

In the present article we report on the synthesis of 2-(aryloxymethyl)oxiranes and their oxidation with periodic acid to obtain aryloxyacetaldehydes. The latter were converted into the corresponding *N*-cyclohexyl imines which were reduced to amines with sodium tetrahydridoborate. *N*-(Aryloxyethyl)cyclohexanamines were isolated and characterized as hydrochlorides.

By heating substituted phenols with excess 2-(chloromethyl)oxirane in aqueous sodium hydroxide we obtained the corresponding 2-(aryloxymethyl)-

Scheme 1.



Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 1-naphthyl (**f**).

oxiranes **Ia**–**If** in 57–78% yields (Scheme 1). The optimal amount of sodium hydroxide was 1.5 equiv (with respect to initial phenol); when the amount of alkali was smaller, the reaction was accompanied by formation of 3-aryloxy-1-chloropropan-2-ols as by-products.

The oxidation of oxiranes **Ia**–**If** with periodic acid in aqueous dioxane on heating gave aryloxyacetaldehydes **IIa**–**IIf** in 41–73% yield. The reactions were complete in 30–40 min at optimal temperature. The structure of aldehydes **IIa**–**IIf** was confirmed by the ^{1}H NMR spectra which contained signals typical of aldehyde protons at δ 9.69–9.80 ppm. Aromatic protons resonated in the region δ 6.42–8.20 ppm, and signals from the methylene protons appeared at δ 4.41–4.69 ppm. Compounds **IIb** and **IIc** also displayed signals from methyl protons at δ 2.23 and 2.20 ppm, respectively, and the hydroxymethyl group in **IId** gave a signal at δ 3.77 ppm.

According to the GC–MS data, aryloxyacetaldehydes **IIa**–**IIf** reacted with cyclohexanamine in THF to form the corresponding Schiff bases in almost quantitative yield (reaction time 12–18 h), and the subsequent reduction (without isolation) with sodium tetrahydridoborate in acetic acid afforded 68–75% of amines **IIIa**–**IIIf**. The molecular ion peaks in the mass spectra of **IIIa**–**IIIf** had low intensity, and the base peak was that with *m*/*z* 112 $[CH_2{=}NHC_6H_{11}]^+$. Amines **IIIa**–**IIIf** were isolated and characterized as hydrochlorides **IVa**–**IVf**. In the ^{1}H NMR spectra of **IVa**–**IVf** we observed a complex multiplet at δ 1.00–1.20 ppm due to methylene protons in the cyclohexane ring. Triplets at δ 2.50 and 4.26–4.48 ppm were assigned to the N^+CH_2 and OCH_2 groups, respectively, and the N^+CH and N^+H_2 protons resonated as broadened singlets at δ 2.98–3.20 and 9.10–9.37 ppm, respectively.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in $CDCl_3$ (**IIa**–**IIf**) or DMSO-d_6 (**IIIa**–**IIIf**) on a Bruker DPX spectrometer operating at 400 MHz; tetramethylsilane was used as internal reference. The IR spectra were measured on an FSM-1201 spectrometer with Fourier transform from films (liquids) or KBr pellets (crystalline substances). Thin-layer chromatography was performed on a Sorbfil plates (STKh-1A silica gel, layer thickness 110 μm, polyethylene terephthalate support, UV-254 indicator; eluent chloroform; development with iodine vapor or UV light). Gas chromatographic–mass spectrometric analysis was performed on a TRACE GC Ultra instrument with a mass-selective detector [TR-5MS SQC quartz capillary column, 15 m×0.25 mm, film thickness 0.25 μm; injector temperature 200°C; oven temperature programming from 40°C (1 min) to 200°C at a rate of 30 deg/min; carrier gas helium, flow rate 1 ml/min; interface temperature 200°C; quadrupole temperature 200°C; electron impact, 70 eV].

Oxiranes Ia–If (*general procedure***).** A solution of 0.2 mol of phenol in 45.6 g (0.5 mol) of 2-(chloromethyl)oxirane was heated to 82–85°C, a solution of 12.0 g (0.3 mol) of sodium hydroxide in 30 ml of water was added dropwise over a period of 1 h under vigorous stirring, and the mixture was stirred at that temperature until complete conversion of the initial phenol. The organic phase was separated from the hot mixture, washed with hot water (40 ml) and a saturated aqueous solution of sodium chloride until neutral reaction, dried over Na_2SO_4, and filtered. Excess 2-(chloromethyl)oxirane was distilled off under reduced pressure (20–25 mm), and the residue was distilled in a vacuum (**Ia**–**Ic**, **If**) or recrystallized (**Id**, **Ie**).

2-(Phenoxymethyl)oxirane (Ia) was synthesized from 18.8 g of phenol; reaction time 3 h. Yield 19.6 g (65%), colorless liquid, bp 96–98°C (4 mm), n_D^{20} = 1.5306; published data [12]: bp 92°C (1 mm), n_D^{20} = 1.5318.

2-(2-Methylphenoxymethyl)oxirane (Ib) was synthesized from 21.6 g of 2-methylphenol; reaction time 2.5 h. Yield 20.4 g (62%), colorless liquid, bp 99–102°C (4 mm), n_D^{20} = 1.5270; published data [13]: bp 262–263°C.

2-(4-Methylphenoxymethyl)oxirane (Ic) was synthesized from 21.6 g of 4-methylphenol; reaction time 3.5 h. Yield 25.5 g (78%), colorless liquid, bp 107–109°C (5 mm), n_D^{20} = 1.5260; published data [12]: bp 98°C (2 mm), n_D^{20} = 1.5272.

2-(4-Methoxyphenoxymethyl)oxirane (Id) was synthesized from 24.8 g of 4-methoxyphenol; reaction time 3 h. Yield 25.9 g (78%), colorless rhombic crystals, mp 47–49°C (from petroleum ether); published data: [14]: mp 48–48.5°C.

2-(4-Nitrophenoxymethyl)oxirane (Ie) was obtained from 27.8 g of 4-nitrophenol; reaction time 9 h. Yield 24.6 g (63%), light yellow crystals, mp 67.5–68.5°C (from *i*-PrOH); published data [12]: mp 64°C.

2-(Naphthalen-1-yloxymethyl)oxirane (If) was obtained from 28.8 g of 1-naphthol; reaction time 11 h. Yield 22.8 g (57%), light yellow oily substance, bp 162–165°C (4 mm), n_D^{20} = 1.6110; published data [15]: bp 118–122°C (0.25 mm), n_D^{24} = 1.6112.

Aldehydes **IIa**–**IIf** were synthesized according to the procedure described in [11].

Phenoxyacetaldehyde (IIa) was synthesized from 11.2 g (0.075 mol) of compound **Ia** using 17.1 g (0.075 mol) of periodic acid in 65 ml of water at 50°C; reaction time 45 min. Yield 6.5 g (64%), colorless oily substance, bp 79–82°C (6 mm), n_D^{20} = 1.5350; published data [11]: bp 69–73°C (2 mm), n_D^{20} = 1.5380. IR spectrum, ν, cm^{-1}: 2820, 2720 (C–H, aldehyde); 1740 (C=O). ^1H NMR spectrum, δ, ppm: 4.41 s (2H, CH_2), 6.76–7.21 m (5H, H_{arom}), 9.69 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 136 (39.1) $[M]^+$, 107 (50.5), 94 (4.0), 77 (100), 65 (8.9), 51 (28.7).

(2-Methylphenoxy)acetaldehyde (IIb) was synthesized from 9.0 g (0.055 mol) of compound **Ib** using 12.7 g (0.055 mol) of periodic acid in 50 ml of water at 50°C; reaction time 1.5 h. Yield 4.33 g (53%), yellow oily substance, bp 80.5–84.5°C (2 mm), n_D^{20} = 1.5205. IR spectrum, ν, cm^{-1}: 2827, 2725 (C–H, aldehyde); 1735 (C=O). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, *o*-CH_3), 4.54 s (2H, CH_2), 6.64–7.16 m (4H, H_{arom}), 9.85 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 150 (90.6) $[M]^+$, 121 (62.3), 108 (10.3), 107 (26.6), 91 (100), 77 (23.9), 65 (27.7). Found, %: C 71.72; H 6.66. $C_9H_{10}O_2$. Calculated, %: C 71.98; H 6.71. *M* 150.17.

(4-Methylphenoxy)acetaldehyde (IIc) was synthesized from 8.2 g (0.05 mol) of compound **Ic** using 11.4 g (0.05 mol) of periodic acid in a mixture of 50 ml of water and 20 ml of dioxane at 55°C; reaction time 40 min. Yield 3.95 g (53%), yellow oily substance, bp 87–92°C (3 mm), n_D^{20} = 1.5269. IR spectrum, ν, cm^{-1}: 2822, 2720 (C–H, aldehyde); 1740 (C=O). ^1H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 4.41 s (2H, CH_2), 6.68–6.71 m (2H, H_{arom}), 6.99–7.01 m (2H, H_{arom}), 9.72 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 150 (83.1) $[M]^+$, 121 (92.6), 108 (7.6), 107 (8.5), 91 (100), 77 (28.2), 65 (24.1). Found, %: C 71.72; H 6.90. $C_9H_{10}O_2$. Calculated, %: C 71.98; H 6.71. *M* 150.17.

(4-Methoxyphenoxy)acetaldehyde (IId) was synthesized from 8.5 g (0.047 mol) of compound **Id** using 17.1 g (0.05 mol) of periodic acid in a mixture of 50 ml of water and 20 ml of dioxane at 45°C; reaction time 20 min. Yield 5.69 g (73%), yellow oily substance, bp 138–142°C (2 mm), n_D^{20} = 1.5393. IR spectrum, ν, cm^{-1}: 2835, 2715 (C–H, aldehyde); 1740 (C=O). ^1H NMR spectrum, δ, ppm: 3.77 s (3H, CH_3O), 4.52 s (2H, CH_2), 6.84 s (4H, H_{arom}), 9.84 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 166 (96.2) $[M]^+$, 137 (28.9), 108 (10.3), 123 (100), 107 (18.9), 95 (19.7), 77 (37.3). Found, %: C 64.65; H 6.14. $C_9H_{10}O_3$. Calculated, %: C 65.05; H 6.07. *M* 166.17.

(4-Nitrophenoxy)acetaldehyde (IIe) was synthesized from 9.75 g (0.05 mol) of compound **Ie** using 11.4 g (0.05 mol) of periodic acid in a mixture of 45 ml of water and 20 ml of dioxane at 50°C; reaction time 35 min. Yield 3.7 g (41%), light yellow crystals, bp 175–182°C (3 mm), mp 73–74°C. IR spectrum, ν, cm^{-1}: 2820, 2730 (C–H, aldehyde); 1750 (C=O). ^1H NMR spectrum, δ, ppm: 4.67 s (2H, CH_2), 6.91 d (2H, H_{arom}, *J* = 9.3 Hz), 8.14 d (2H, H_{arom}, *J* = 9.3 Hz), 9.78 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 181 (60.8) $[M]^+$, 152 (100), 122 (18.7), 106 (10.7). Found, %: C 52.95; H 4.02; N 7.83. $C_8H_7NO_4$. Calculated, %: C 53.04; H 3.90; N 7.73. *M* 181.15.

(Naphthalen-1-yloxy)acetaldehyde (IIf) was synthesized from 7.0 g (0.035 mol) of compound **If** and 8.0 g (0.035 mol) of periodic acid in a mixture of 40 ml of water and 15 ml of dioxane at 55°C; reaction time 1.5 h. Yield 2.81 g (43%), orange oily substance, bp 150–156°C (3 mm), n_D^{20} = 1.6205; published data [16]: bp 120–125°C (0.04 mm). IR spectrum, ν, cm^{-1}: 2820, 2722 (C–H, aldehyde); 1735 (C=O). ^1H NMR spectrum, δ, ppm: 4.49 s (2H, CH_2), 6.42–8.20 m (7H, H_{arom}), 9.76 s (1H, CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 186 (100) $[M]^+$, 157 (37.0), 143 (44.2), 127 (38.2), 115 (73.1).

Amine hydrochlorides IVa–IVf (*general procedure*). A solution of 6.1 mmol of aldehyde **IIa**–**IIf** in 20 ml of tetrahydrofuran was added under nitrogen to a solution of 630 mg (6.4 mmol) of cyclohexanamine in 5 ml of THF, and the mixture was stirred for 1 h at room temperature and was then kept for 18 h at 4°C. The mixture was cooled to 0°C, 180 mg (4.5 mmol) of sodium tetrahydridoborate was added, the mixture was stirred until gas evolution ceased, a solution of 180 mg (3.0 mmol) of acetic acid in 5 ml of THF was added dropwise over a period of 40 min, and the mixture was stirred for 45 min. The mixture was treated with 25 ml of a 10% aqueous solution of sodium hydroxide and extracted with diethyl ether, the extract was dried over $MgSO_4$ and filtered, the filtrate was cooled to 0°C, a solution of hydrogen chloride in diethyl ether was added, and the precipitate was filtered off.

***N*-(2-Phenoxyethyl)cyclohexanamine hydrochloride (IVa).** Yield 1.11 g (71%), colorless needles, mp 168–170°C. ^1H NMR spectrum, δ, ppm: 1.01–2.12 m (10H, (CH_2), 2.50 t (2H, N^+CH_2, *J* = 1.8 Hz), 2.99–3.08 br.s (1H, N^+CH), 4.29 t (2H, OCH_2, *J* = 5.2 Hz), 6.96–7.34 m (5H, H_{arom}), 9.10–9.21 br.s (2H, N^+N_2). Mass spectrum of free amine **IIIa**, *m*/*z* (I_{rel}, %): 219 (5.9) $[M]^+$, 176 (11.9), 112 (100). Found, %:

C 65.51; H 8.42; N 5.56. $C_{14}H_{21}NO \cdot HCl$. Calculated, %: C 65.74; H 8.67; N 5.48. *M* 219.32.

***N*-[2-(2-Methylphenoxy)ethyl]cyclohexanamine hydrochloride (IVb).** Yield 1.02 g (62%), colorless crystals, mp 160–162°C. ^{1}H NMR spectrum, δ, ppm: 1.07–2.15 m (10H, CH_2), 2.22 s (3H, CH_3), 2.50 t (2H, N^+CH_2, *J* = 1.9 Hz), 3.06–3.14 br.s (1H, N^+CH), 4.30 t (2H, OCH_2, *J* = 5.3 Hz), 6.86–7.18 m (4H, H_{arom}), 9.13–9.24 br.s (2H, N^+H_2). Mass spectrum of free amine **IIIb**, *m*/*z* (I_{rel}, %): 233 (23.8) $[M]^+$, 190 (15.8), 112 (100). Found, %: C 66.88; H 8.85; N 5.08. $C_{15}H_{23}NO \cdot HCl$. Calculated, %: C 66.77; H 8.97; N 5.19. *M* 233.35.

***N*-[2-(4-Methylphenoxy)ethyl]cyclohexanamine hydrochloride (IVc).** Yield 1.21 g (74%), white crystals, mp 159–160°C. ^{1}H NMR spectrum, δ, ppm: 1.06–2.11 m (10H, CH_2), 2.24 s (3H, CH_3), 2.50 t (2H, N^+CH_2, *J* = 1.8 Hz), 2.95–3.06 br.s (1H, N^+CH), 4.27 t (2H, OCH_2, *J* = 5.4 Hz), 6.88 d (2H, H_{arom}, *J* = 8.6 Hz), 7.12 d (2H, H_{arom}, *J* = 8.2 Hz), 9.27–9.36 br.s (2H, N^+H_2). Mass spectrum of free amine **IIIc**, *m*/*z* (I_{rel}, %): 233 (12.8) $[M]^+$, 190 (12.8), 112 (100). Found, %: C 66.51; H 8.82; N 5.09. $C_{15}H_{23}NO \cdot HCl$. Calculated, %: C 66.77; H 8.97; N 5.19. *M* 233.35.

***N*-[2-(4-Methoxyphenoxy)ethyl]cyclohexanamine hydrochloride (IVd).** Yield 1.17 g (67%). colorless crystals, mp 140–142°C. ^{1}H NMR spectrum, δ, ppm: 1.08–2.11 m (10H, CH_2), 2.51 t (2H, N^+CH_2, *J* = 1.9 Hz), 2.98–3.06 br.s (1H, N^+CH), 3.71 s (3H, OCH_3), 4.25 t (2H, OCH_2, *J* = 5.3 Hz), 6.87–6.95 m (4H, H_{arom}), 9.20–9.32 br.s (2H, N^+H_2). Mass spectrum of free amine **IIId**, *m*/*z* (I_{rel}, %): 249 (10.1) $[M]^+$, 206 (8.2), 126 (67.0), 112 (100). Found, %: C 62.34; H 8.32; N 5.08. $C_{15}H_{23}NO_2 \cdot HCl$. Calculated, %: C 63.04; H 8.46; N 4.90. *M* 249.35.

***N*-[2-(4-Nitrophenoxy)ethyl]cyclohexanamine hydrochloride (IVe).** Yield 1.36 g (74%), light yellow crystals, mp 205.5–207°C. ^{1}H NMR spectrum, δ, ppm: 1.05–2.13 m (10H, CH_2), 2.50 t (2H, N^+CH_2, *J* = 1.7 Hz), 3.00–3.11 br.s (1H, N^+CH), 4.47 t (2H, OCH_2, *J* = 5.1 Hz), 7.20 d (2H, H_{arom}, *J* = 9.1 Hz), 8.24 d ($2H_{arom}$, *J* = 9.3 Hz), 9.26–9.39 br.s (2H, N^+H_2). Mass spectrum of free amine **IIIe**, *m*/*z* (I_{rel}, %): 264 (1.7) $[M]^+$, 221 (24.8), 112 (100). Found, %: C 55.72; H 7.21; N 9.09. $C_{14}H_{20}N_2O_3 \cdot HCl$. Calculated, %: C 55.90; H 7.04; N 9.31. *M* 264.32.

***N*-[2-(Naphthalen-1-yloxy)ethyl]cyclohexanamine hydrochloride (IVf).** Yield 1.31 g (70%), colorless crystals, mp 237–238°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 1.06–2.20 m (10H, CH_2), 2.50 t (2H, N^+CH_2), 3.07–3.18 br.s (1H, N^+CH), 4.48 t (2H, OCH_2, *J* = 5.0 Hz), 6.99 d (1H, 2-H, *J* = 7.5 Hz), 7.44 d (1H, 4-H, *J* = 7.8 Hz), 7.50–7.57 m (3H, 3-H, 6-H, 7-H), 7.88 d (1H, 5-H, *J* = 6.8 Hz), 8.37 d (1H, 8-H, *J* = 7.5 Hz), 9.30– 9.37 br.s (2H, N^+H_2). Mass spectrum of free base **IVf**, *m*/*z* (I_{rel}, %): 269 (16.1) $[M]^+$, 226 (7.0), 126 (66.4), 112 (100). Found, %: C 70.55; H 8.09; N 4.62. $C_{18}H_{23}NO \cdot HCl$. Calculated, %: C 70.69; H 7.91; N 4.58. *M* 269.38.

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