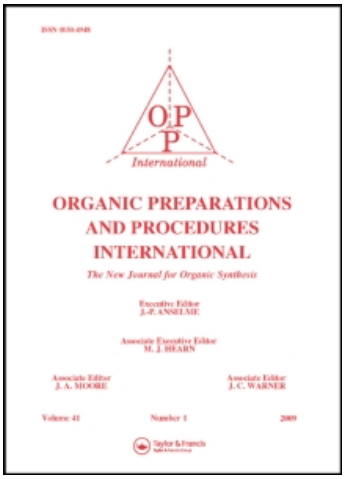

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PREPARATION OF PHENYLGLYCOLIC ACIDS AND SODIUM *p*-(N,N-DIALKYLAMINO)PHENYLGLYCOLATES

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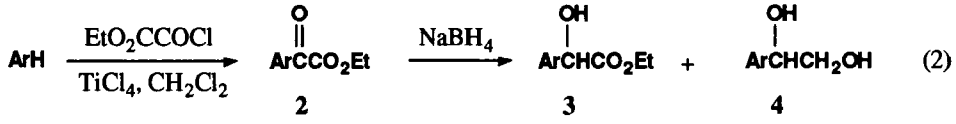
Phenylglycolic acid derivatives, especially esters, have found applications as pharmaceuticals owing to their wide physiological activity. They have recently been shown to possess interesting anti-muscarinic,[1] antihypertensive,[2] antiallergic[3] and antihistaminic[4] activities. Other esters of phenylglycolic acid have been used as repellents of flour beetles[5] or as additives for thermal recording materials.[6]

Neither of the two routes to barium *p*-(N,N-dimethylamino)phenylglycolate is convenient. The first proceeds by the addition of hydrogen cyanide to *p*-(N,N-dimethylamino)benzaldehyde, hydrolysis of the resulting nitrile with concentrated sulfuric acid to the corresponding benzamide and subsequent hydrolysis with barium hydroxide to barium *p*-(N,N-dimethylamino)phenylglycolate.[7] The second method involves condensation of N,N-dimethylaniline with chloral and hydrolysis of the obtained 1-[*p*-(dimethylamino)phenyl]-2,2,2-trichloroethanol with sodium hydroxide.[8] A third route proceeds by condensation of N,N-dimethylaniline with methyl α,β-dioxobutyrate and cleavage of the α-acetyl-*p*-(N,N-dimethylamino)phenylglycolic acid thus obtained with potassium hydroxide to afford the final product as the potassium salt.[9] The use of *p*-(N,N-dimethylamino)phenylglycolic acid (as pyrylium mandelates) in silver-free recording materials is described in a patent.[10] From the literature, the best method for the preparation of *p*-alkyl- and *p*-alkoxyphenylglycolic acids appears to be a phase-transfer catalytic reaction of aromatic aldehydes with chloroform and 50% aqueous sodium hydroxide (Eq. 1).[11] Although we successfully applied this procedure for preparation of two new compounds, *p*-hexyl- and *p*-hexyloxyphenylglycolic acids (**1a** and **1b**), attempts to use it for the preparation of *p*-(N,N-dialkylamino)phenylglycolic acids gave complex mixtures.

$$ArCHO + CHCl_3 \xrightarrow[TEBAC]{50\%\ NaOH} \underset{\mathbf{1}}{ArCH(OH)CO_2H} \qquad (1)$$

a) Ar = *p*-(*n*-C_6H_{13})C_6H_4; b) Ar = *p*-(*n*-$C_6H_{13}O$)C_6H_4

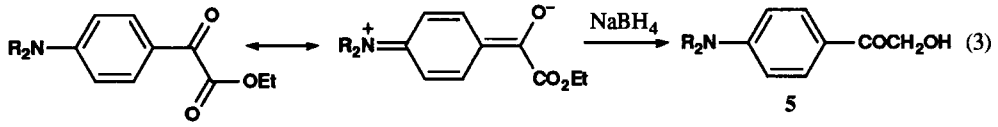
We found that a modification of Kindler's procedure[12] involving condensation of N,N-dialkylanilines with ethyl oxalyl chloride in the presence of aluminum chloride in nitrobenzene, followed by reduction of the ketoester **2** to hydroxyester **3** and finally hydrolysis of **3**, can conveniently be applied to the preparation of *p*-(N,N-dialkylamino)phenylglycolic acids (Eq. 2).



(2)

a) Ar = *p*-$(Me_2N)C_6H_4$; b) Ar = *p*-$(Et_2N)C_6H_4$

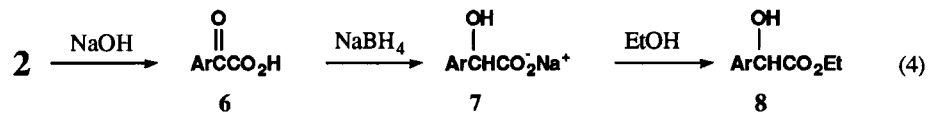
Following this procedure but using titanium tetrachloride in methylene chloride at -10°, we prepared ethyl *p*-(N,N-dimethylamino)- (**2a**)[13] and *p*-(N,N-diethylamino)phenylglyoxylate (**2b**) from the corresponding N,N-dialkylanilines and ethyl oxalyl chloride in 40% and 48% yields, respectively. The reduction of **2a** and **2b** with sodium borohydride in methanol at room temperature gave mixtures of the expected hydroxyesters **3a** and **3b** together with the unexpected vicinal diols **4a** and **4b**. It is probable that the strong coupling of the nitrogen lone pair through the π-system of the aromatic ring strongly decreases the positive charge of the keto carbonyl carbon atom; thus the ester carbonyl group becomes more reactive (Eq. 3) and is reduced first giving the alcohols **5** which are then slowly reduced to the diols (**4**). Deactivation of the ester carbonyl group by hydrolysis to the acid **6**[13]



(3)

R = Me, Et

followed by reduction with sodium borohydride in THF, according to the literature method for reduction of functionalized ketones,[14] afforded sodium salts of *p*-(N,N-dimethylamino)- and *p*-(N,N-diethylamino)phenylglycolic acids (**7a** and **7b**) in 90% and 60% yields, respectively (Eq. 4). Compounds **7** were characterized without conversion to phenylglycolic acids because their acidification gives ionic compounds (zwitterions) which are difficult to extract from aqueous solutions. Salt **7b** appeared to be highly hygroscopic. It can easily be converted into ethyl α-ethoxy-*p*-(N,N-diethylamino)phenylacetate (**8b**) in refluxing ethanol in the presence of sulfuric acid.



(4)

a) Ar = *p*-$(Me_2N)C_6H_4$; b) Ar = *p*-$(Et_2N)C_6H_4$

EXPERIMENTAL SECTION

Melting points were determined with a hot-stage microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are in parts per million (δ) relative to TMS. Coupling constants (J) are in Hertz (Hz).

Phenylglycolic Acids 1. General Procedure.- A 50% aqueous NaOH solution (12.5 mL) was added portionwise at 40° to a solution of benzaldehyde (0.05 mol) and triethylbenzylammonium chloride (0.62g, 0.0025 mol) in $CHCl_3$ (8 mL). Then the mixture was stirred at 58° for 6 hrs. After cooling, the reaction mixture was poured into water (300 mL) and extracted with diethyl ether (2 x 70 mL). The aqueous layer was acidified with 50% H_2SO_4 and extracted with diethyl ether (4 x 80 mL). The solvent was evaporated and the residue was recrystallized from benzene.

***p*-Hexylphenylglycolic Acid (1a)**, colorless solid (2.07g, 18% yield), mp. 106-107°. ^1H NMR: δ 0.88 (m, 3H), 1.29 (m, 6H), 1.58 (m, 2H), 2.58 (t, 2H, J = 9.0), 5.17 (s, 1H), 7.15 (d, 2H, J = 9.0), 7.29 (d, 2H, J = 9.0). ^{13}C NMR: δ 14.1, 22.5, 29.0, 31.3, 31.7, 35.6, 72.5, 126.5 (2C), 128.8 (2C), 134.5, 143.8, 178.0 (C=O).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.16; H, 8.67

***p*-Hexyloxyphenylglycolic Acid (1b)**, colorless solid (4.63g, 37% yield), mp. 92.5-93.5°. ^1H NMR: δ 0.90 (t, 3H, J = 6.9), 1.38 (m, 6H), 1.75 (m, 2H), 3.93 (t, 2H, J = 6.5), 5.07 (s, 1H), 6.86 (d, 2H, J = 8.7), 7.35 (d, 2H, J = 8.6), 7.18 (bs, 2H, OH). ^{13}C NMR: δ 13.8, 22.4, 25.5, 29.0, 31.3, 67.8, 72.0 (2C), 114.2 (2C), 127.7 (2C), 130.8, 158.9, 175.3 (C=O).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.82; H, 7.98

Ethyl *p*-(N,N-Dialkylamino)phenylglyoxylates 2. General Procedure.- Ethyl oxalyl chloride (15.0 g, 0.11 mol) was added to a solution of the N,N-dialkylaniline (0.10 mol) in CH_2Cl_2 (150 mL) at -10° and then $TiCl_4$ (41.74 g, 0.22 mol) was added dropwise at -15°. The reaction mixture was stirred at -10° for 4 hrs, poured into ice (400 g) and the layers were separated. The aqueous layer was extracted with diethyl ether (6 x 100 mL), the combined organic extracts were washed with water, 10% solution of Na_2CO_3, water again and dried over $MgSO_4$. After removal of the solvents the crude product was sufficiently pure to be used directly in the next step.

Ethyl *p*-(N,N-Dimethylamino)phenylglyoxylate (2a), yellow prisms (8.85 g, 40% yield), mp. 93°, lit.[13] mp. 95°. ^1H NMR: δ 1.41 (t, 3H, J = 7.2), 3.10 (s, 6H), 4.41 (q, 2H, J = 7.2), 6.66 (d, 2H, J = 9.0), 7.90 (d, 2H, J = 9.0). ^{13}C NMR: δ 14.1, 40.0 (2C), 61.7, 110.8 (2C), 120.2, 132.5 (2C), 154.5, 165.0 (O-C=O), 184.1 (C=O).

Ethyl *p*-(N,N-Diethylamino)phenylglyoxylate (2b), yellow oil (11.94 g, 48% yield), purification by column chromatography (silica gel/$CHCl_3$) gave an analytical sample. ^1H NMR: δ 1.20 (t, 6H, J = 7.1), 1.40 (t, 3H, J = 7.1), 3.44 (q, 4H, J = 7.1), 4.41 (q, 2H, J = 7.1), 6.64 (d, 2H, J = 9.3), 7.87 (d, 2H, J = 9.3). ^{13}C NMR: δ 12.3 (2C), 14.1, 44.7 (2C), 61.6, 110.5 (2C), 119.5, 132.7 (2C), 152.3, 165.0 (O-C=O), 183.7 (C=O).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.37; H, 7.72; N, 5.51

Reduction of Ethyl *p*-(N,N-Dialkylamino)phenylglyoxylate 2 with $NaBH_4$. General Procedure.- To a stirred solution of ester **2** (0.0045 mol) in methanol (10 mL) was added portionwise $NaBH_4$ (0.2 g, 0.005 mol) at 20°. The reaction mixture was stirred continuously for 0.5 hr, poured into ice-water (20 g) and extracted with $CHCl_3$. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography (silica gel/$CHCl_3$) to give α-hydroxyester **3** (R_f 0.32, **3a**) and diol **4** (R_f 0.05, **4a**).

Ethyl *p*-(N,N-Dimethylamino)phenylglycolate (3a), colorless solid (0.51 g, 51% yield), mp. 76°. ^{1}H NMR: δ 1.22 (t, 3H, J = 7.0), 2.94 (s, 6H), 3.35 (d, 1H, J = 5.4), 4.19 (dq, 1H, J = 10.8 and J = 8.6), 4.20 (dq, 1H, J = 10.8 and J = 8.6), 5.05 (d, 1H, J = 4.9), 6.71 (d, 2H, J = 8.8), 7.25 (d, 2H, J = 8.8). ^{13}C NMR: δ 14.0, 40.3 (2C), 61.7, 72.6, 112.2 (2C), 126.1, 127.4 (2C), 150.5, 174.0 (C=O).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.68; N, 6.24

***p*-(N,N-Dimethylamino)phenyl-1,2-ethanediol (4a)**, colorless solid (0.32 g, 40% yield), mp. 81-82°. ^{1}H NMR: δ 2.91 (s, 6H), 3.30 (sb, 2H, OH), 3.61 (d, 2H, J = 6.8), 4.65 (t, 1H, J = 6.8), 6.68 (d, 2H, J = 8.7), 7.18 (d, 2H, J = 8.7). ^{13}C NMR: δ 40.6 (2C), 67.9, 74.4, 112.5 (2C), 127.1, 128.4 (2C), 150.3.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.88; H, 8.32; N, 7.50

Ethyl *p*-(N,N-Diethylamino)phenylglycolate (3b), colorless oil (0.79g, 70% yield). ^{1}H NMR: δ 1.14 (t, 6H, J = 7.0), 1.22 (t, 3H, J = 7.0), 3.33 (q, 4H, J = 7.0), 4.19 (dq, 1H, J = 10.8 and J = 8.6), 4.20 (dq, 1H, J = 10.8 and J = 8.6), 5.03 (d, 1H, J = 4.3), 6.63 (d, 2H, J = 8.9), 7.21 (d, 2H, J = 8.9). ^{13}C NMR: δ 12.4 (2C), 14.0, 44.2 (2C), 61.7, 72.7, 111.4 (2C), 124.9, 127.7 (2C), 147.7, 174.1 (C=O).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.80; H, 8.45; N, 5.62

***p*-(N,N-Diethylamino)phenyl-1,2-ethanediol (4b)**, colorless solid (0.28g, 30% yield), mp. 101-102°. ^{1}H NMR: δ 1.15 (t, 6H, J = 7.0), 2.35 (sb, 2H, OH), 3.35 (q, 4H, J = 7.0), 3.69 (d, 2H, CH_2O, J = 6.2), 4.69 (t, 1H, J = 6.0), 6.65 (d, 2H, J = 8.7), 7.19 (d, 2H, J = 8.7). ^{13}C NMR: δ 12.5 (2C), 44.3 (2C), 67.9, 74.5, 111.6 (2C), 126.9, 127.4 (2C), 147.7.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.96; H, 9.20; N, 6.59

***p*-(N,N-Dialkylamino)phenylglyoxylic Acids 6. General Procedure.**- A mixture of ethyl *p*-(N,N-dialkylamino)phenylglyoxylate (**2**, 0.05 mol) and 10% NaOH (30 mL) was stirred at 20° for 6 hrs and product was neutralized with 10% HCl. The solid acid was collected, washed with cold water and dried.

***p*-(N,N-Dimethylamino)phenylglyoxylic Acid (6a)**, light yellow solid (8.0 g, 83% yield), mp. 186-187°, lit.[13] mp. 187°. ^{1}H NMR: δ 3.05 (s, 6H), 6.72 (d, 2H, J = 9.0), 7.74 (d, 2H, J = 9.0). ^{13}C NMR: δ 39.5 (2C), 110.7 (2C), 119.5, 131.4 (2C), 153.9, 168.1 (O-C=O), 187.6 (C=O).

***p*-(N,N-Diethylamino)phenylglyoxylic Acid (6b)**, yellow solid (9.05 g, 82% yield), mp. 102-103°. ^{1}H NMR: δ 1.22 (t, 6H, J = 7.0), 3.46 (q, 4H, J = 7.0), 6.65 (d, 2H, J = 9.4), 8.30 (d, 2H, J = 9.4), 10.31 (s, 1H). ^{13}C NMR: δ 12.4 (2C), 44.8 (2C), 110.8 (2C), 118.8, 134.6 (2C), 152.9, 163.1 (HO-C=O), 180.0 (C=O).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.47; H, 7.01; N, 6.33

Sodium *p*-(N,N-Dialkylamino)phenylglycolate 7. General Procedure.- To a stirred suspension of

the p-(N,N-dialkylamino)phenylglyoxylic acid (**6**, 0.05 mol) in THF (50 mL) was added portionwise $NaBH_4$ (1.89 g, 0.05 mol) at 0°. The reaction mixture was stirred at 20° for 8 hrs and the solid product was recrystallized from ethanol.

Sodium *p*-(N,N-Dimethylamino)phenylglycolate (7a), colorless solid (9.7 g, 90% yield), mp. 248-249° (dec.). ^{1}H NMR: δ 2.82 (s, 6H), 4.41 (d, 1H, J = 4.5), 4.87 (d, 1H, J = 4.5), 6.61 (d, 2H, J = 9.0), 7.18 (d, 2H, J = 9.0. ^{13}C NMR: δ 40.6 (2C), 73.4, 118.9 (2C), 127.1 (2C), 132.2, 149.2, 175.9 (C=O).

Anal. Calcd. for $C_{10}H_{12}NO_3Na$: C, 55.30; H, 5.57; N, 6.45. Found: C, 55.28; H, 5.49; N, 6.35

Sodium *p*-(N,N-Diethylamino)phenylglycolate (7b), colorless solid (7.3 g, 60% yield), mp. 188-189° (dec.). ^{1}H NMR: δ 0.76 (t, 3H, J = 6.9), 2.97 (q, 4H, J = 6.9), 4.58 (s, 1H), 6.61 (d, 2H, J = 8.2), 7.00 (d, 2H, J = 8.2). ^{13}C NMR: δ 12.9 (2C), 46.3 (2C), 76.1, 116.8 (2C), 129.6 (2C), 131.7, 149.6, 180.9 (C=O); it was not sufficiently stable to be submitted for analysis.

Ethyl α-Ethoxy-*p*-(N,N-diethylamino)phenylacetate (8).- A mixture of sodium *p*-(N,N-diethylamino)phenylglycolate (**7b**, 2.45 g, 0.01 mol), ethanol (10 mL) and H_2SO_4 (d = 1.84) (1.4 mL, 0.025 mol) was refluxed for 2 hrs. After evaporation of the excess ethanol, the residue was dissolved in ethyl acetate and washed with water, 10% $NaHCO_3$, water again and dried over Na_2CO_3. Removal of the solvent gave **8** as a pure colorless oil (1.67 g, 60% yield). ^{1}H NMR: δ 1.15 (t, 6H, NEt_2, J = 7.0), 1.23 (t, 3H, CO_2Et, J = 7.0), 1.25 (t, 3H, OEt, J = 7.0), 3.34 (q, 4H, J = 7.0), 3.51 (m, 2H, CO_2Et), 4.12 (dq, 1H, OEt, J = 10.7 and J = 8.2), 4.22 (dq, 1H, OEt, J = 10.8 and J = 8.2), 4.74 (s, 1H), 6.63 (d, 2H, J = 9.0), 7.26 (d, 2H, J = 9.0). ^{13}C NMR: δ 12.5 (2C), 14.1, 15.1, 44.2 (2C), 60.8, 64.6, 80.7, 111.3 (2C), 122.9, 128.5 (2C), 147.9, 171.6 (C=O).

Anal. Calcd. for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.52; H, 9.03; N, 5.02

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