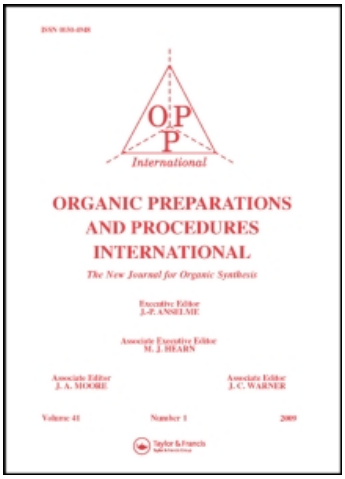

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SYNTHESIS AND OPTICAL RESOLUTION OF 1-(1-NAPHTHYL)-2-DIMETHYLAMINOETHANOL

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SYNTHESIS AND OPTICAL RESOLUTION OF 1-(1-NAPHTHYL)-2-DIMETHYLAMINOETHANOL

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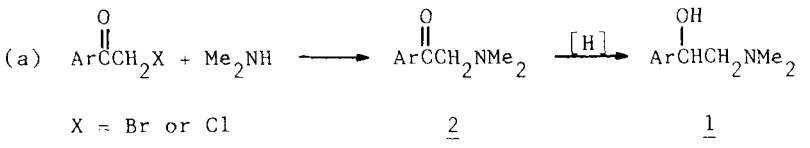
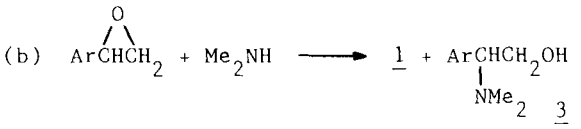
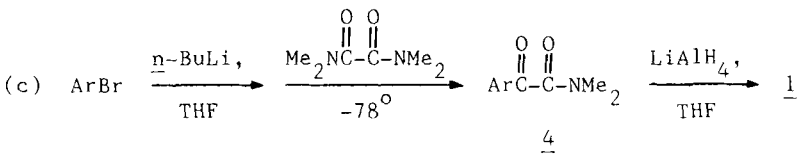
1-Aryl-2-dimethylaminoethanols (1) are of interest inasmuch as these structures occur in a variety of biologically active natural and synthetic products.[1,2] Three general synthetic routes to 1 (or, more specifically to 1a, where Ar = 1-naphthyl) have been reported.[1-4]





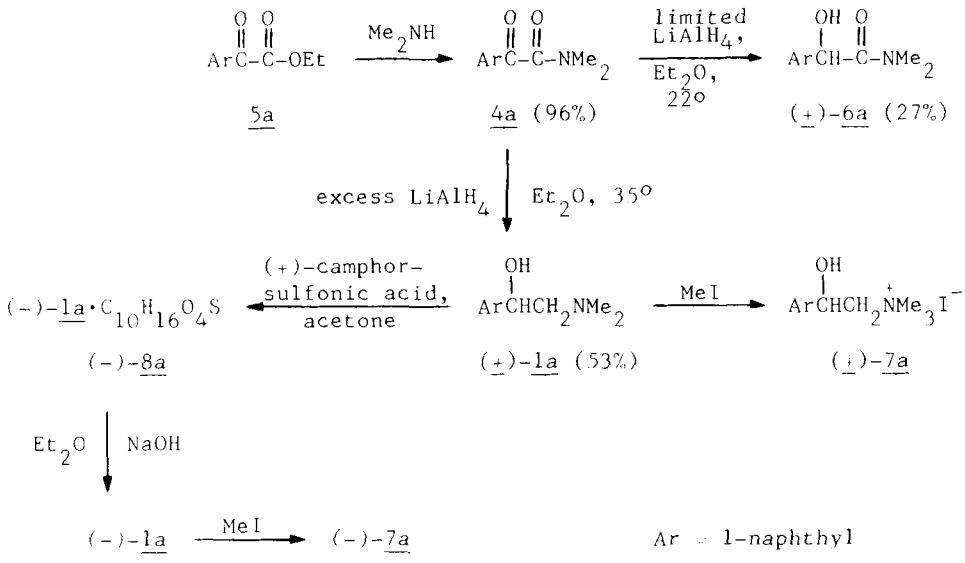


Using route a, Howe et al.[2] obtained only a 20-30% yield of ketoamines 2, while King and Work[3] experienced difficulty in purification of 1. Method b was complicated by the fact that two products (1 and 3) were formed,[2] while method c gave yields of 15-92% of the glyoxylamide 4.[1]

In particular, for the case of Ar = 1-naphthyl, a low yield of 38% (for 4a) was ascribed to steric hindrance by the Ar group. The most successful preparation of racemic 1a was reported by Chapman and Triggle[4] who brominated 1-acetylnaphthalene and then followed route a. The aminoketone 2a was isolated as a hydrochloride salt, which was reduced directly by aluminum isopropoxide to liquid 1a (overall yield for 3 steps, 44%).

We now describe the syntheses of both crystalline racemic and optically active 1a, as well as their methiodides, as outlined in SCHEME I.

SCHEME I



The starting material for this scheme was actually diethyl oxalate which was successfully half-hydrolyzed to ethyl potassium oxalate,[5] converted to ethyl oxalyl chloride,[6,7] and then (by Friedel-Crafts reaction on naphthalene, plus separation of isomers)[8] to ketoester 5a. Compound 5a reacted with dimethylamine readily to give a high yield of ketoamide 4a, reducible by means of slightly more than an equivalent amount of lithium aluminum hydride to racemic hydroxy amide 6a or by an excess (4 equivalents) of the reagent to racemic 1a. Treatment of (±)-1a with

(+)-camphorsulfonic acid in acetone permitted the separation (after a number of recrystallizations) of (-)-1a camphorsulfonate, (-)-8a, $[\alpha]_D$ -18°, from which (-)-1a, $[\alpha]_D$ -158°, was easily isolated. The methiodide of (-)-1a (i.e. (-)-7a) showed a rotation of $[\alpha]_D$ -77°.[9]

The 300 MHz ^{1}H NMR spectrum of (±)-1a exhibited a clear resolution of the ABC spin system in the $HOCH_CCH_AH_BN$ structural unit of the molecule, wherein J_{AB} = 12 Hz, J_{BC} = 9 Hz, and J_{AC} = 3 Hz in acetone-d_6 as a solvent. The use of DMSO-d_6/acetone-d_6 as solvent for (±)-7a and of DMSO-d_6 alone for (-)-7a served to decrease part of this resolution but still permitted assignment of some coupling constants.

At an inlet temperature of 140° and with impact by 70-volt electrons, compounds 1a, 4a, and 6a gave mass spectral molecular ions of only low intensity. The most abundant ions were $CH_2{=}\overset{+}{N}Me_2$, naphthyl$^+$, and naphthalene•H$^+$, respectively. In fact, the 1a molecular ion dissociated so readily that the voltage had to be decreased to 5 before the $CH_2{=}\overset{+}{N}Me_2$ peak (m/e 58) came on scale.

EXPERIMENTAL SECTION

Infrared spectra were determined by means of a Perkin-Elmer model 137 Infracord spectrophotometer; optical rotations, by means of a Hilger polarimeter using the sodium D-line; and ^{1}H NMR spectra, by means of a General Electric QE-300 instrument. Mass spectra were recorded by Dr. Richard Wielesek of this laboratory with a CEC model 21-110 apparatus at a source temperature of 140° and (unless otherwise indicated) at 70 eV. Elemental analyses were obtained in the Microanalytical Laboratory, E.T.H., Zürich, Switzerland.

Ethyl Potassium Oxalate.- Absolute ethanol was freed of color-forming substances by refluxing with KOH (40 g./100 ml.) for 15 hr. and then distilled. To an ice-cold, vigorously stirred solution of 71 g. (1.27 mol) of KOH in 450 ml. of purified absolute ethanol was added dropwise 187 g. (1.27 mol) of diethyl oxalate. The mixture was kept in an ice bath overnight and then at room temperature for 2 days. The solvent was removed under reduced pressure. The residue was stirred with ether, collected

by filtration, and dried in air to give 144 g. (73%) of white crystals, mp. 220-222° (dec.), lit.[6] mp. 222-225°.

Ethyl 1-Naphthylglyoxylate (5a).- Ethyl potassium oxalate was converted into ethyl oxalyl chloride,[6,7] which was reacted with naphthalene (Friedel-Crafts) to give a mixture of 5a and its 2-isomer. Isomers were separated as previously described.[8]

N,N-Dimethyl-(1-naphthyl)glyoxylamide (4a).- To a cold (ice-salt bath) solution of 100 g. of ethyl 1-naphthylglyoxylate in 300 ml. of absolute ethanol was added, with swirling, 50 ml. of cold, anhydrous dimethylamine. The mixture was kept at -10° to 0° for 1.5 days and then at room temperature for 3 more days. A small sample of the mixture was evaporated and the residue was triturated with acetone to give seed crystals of 4a. Seeding the mixture and reworking residues from the mother liquor gave 96 g. (96%) of 4a as cream-colored prisms, mp. 99-101°, raised to 100-101.5° on recrystallizations from absolute ethanol, lit.[1] mp. 99-100°. IR (KBr): 1670 (aryl C=O), 1640 (tertiary amide C=O), 786 (C-H out-of-plane bending) cm^{-1}. ^1H NMR (acetone-d_6): δ 3.03 and 3.09 (2 s, 3H each, NMe_2), 7.65 (t, J = 7-8 Hz, 2H, H-6 and H-7), 7.74 (split t, J = 8-9 Hz, 1H, H-3), 8.05 (d, 2H) and 8.26 (d, 1H , H-2, H-4, H-5), 9.20 (d, 1H, H-8). MS m/e (relative intensity): 227 (M^+, 6), 155 (M^+ - $O{=}CNMe_2$, 96), 127 (naphthyl$^+$, 100), 72 ($Me_2\overset{+}{N}{=}C{=}O$, 62).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16

Found: C, 73.90; H, 5.79; N, 6.22

(±)-N,N-Dimethyl-α-hydroxy-α-(1-naphthyl)acetamide (6a).- To a solution of 2.27 g. (0.01 mol) of N,N-dimethyl-(1-naphthyl)glyoxylamide (4a) in 150 ml. of anhydrous ether was added slowly, with swirling, 32 ml. of 0.082 M (0.0026 mol, 4% excess) lithium aluminum hydride in ether. A white precipitate formed immediately. The mixture was allowed to stand

at room temperature for 12 hr. and then treated first with a few ml. of glacial acetic acid and thereafter with water. The ether layer (combined with several ethereal extracts of the aqueous layer) was washed with dilute aqueous sodium hydroxide and then with water, dried (Na_2SO_4), and concentrated to yield 0.61 g. (27%) of (±)-6a, mp. 110-116°. Four recrystallizations (once with charcoal) from ether gave white platelets, mp. 115-117.5°.

IR ($CHCl_3$): 3410 (OH), 1650 (C=O) cm^{-1}. ^1H NMR (acetone-d_6): δ 2.68 and 3.04 (2 s, 3H each, NMe_2), 4.69 (d, J = 6 Hz, OH), 5.98 (d, CHOH), 7.30 (d, J = 9 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.53 and 7.59 (2 overlapping split t, 2H), 7.90 and 7.94 (2 d, 2H), and 8.36 (d, J = 9 Hz, 1H). MS m/e (relative intensity): 229 (M^+, 5), 201 (M^+ - CO, 3), 157 (M^+ - $O{=}CNMe_2$, 64), 129 (naphthalene·H^+, 100), 128 (65), 127 (44), 72 ($Me_2\overset{+}{N}{=}C{=}O$, 74).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11

Found: C, 73.35; H, 6.66; N, 6.15

(±)-1-(1-Naphthyl)-2-dimethylaminoethanol (1a).- Following a method of Micovic and Mihailovic[10] for reduction of N,N-dialkylamides, there was added with stirring and at such a rate as to keep the reaction mixture barely refluxing, a solution of 22.7 g. (0.1 mol) of N,N-dimethyl-(1-naphthyl)glyoxylamide (4a) in 1.5 ℓ. of dry ether to a mixture of 4.0 g. (0.1 mol) of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred and refluxed for 2 hr., cooled in ice, treated successively with 4 ml. of water, 15 ml. of 15% aqueous sodium hydroxide solution, and 12 ml. of water, stirred vigorously for 20 min., and filtered with suction. The precipitate was washed with ether. Combined filtrates were dried (Na_2SO_4), evaporated nearly to dryness, and refrigerated. The colorless plates of (±)-1a which formed were washed with ether and dried in

air, yield 11.4 g. (53%) mp. 62-68.5°, raised to 69-70.5° on recrystallizations from ether, lit.[2] mp. 69-70°.

IR (CCl_4): 3485 (medium, broad in 10% solution, bonded OH), shifted to 3450 cm^{-1} (medium, broad in 0.015% solution). ^1H NMR (acetone-d_6): δ 2.38 (s, 6H, NMe_2), 2.52 (d of d, J_{AB} = 12 Hz, J_{BC} = 9 Hz, 1H, H_B in $HOCH_C-CH_AH_BN$), 2.63 (d of d, J_{AC} = 3 Hz, 1H, H_A), 4.30 (broad s, 1H, OH), 5.54 (d of d, 1H, H_C), 7.4-7.6 (m, 3H), 7.78 (t, J = 7.5 Hz, 2H), 7.90 (d of d, J = 3, 6 Hz, 1H), 8.13 (d, J = 6 Hz, 1H). MS m/e (relative abundance): 215 (M^+, 1), 129 (40), 128 (naphthalene$^+$, 100), 127 (77), 58 ($CH_2{=}\overset{+}{N}Me_2$, >>100); MS (5 eV), 215 (M^+, 7), 58 ($CH_2{=}\overset{+}{N}Me_2$, 100).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51

Found: C, 78.01; H, 8.07; N, 6.49

(±)-1a Methiodide (7a).- This salt was prepared by adding excess methyl iodide to an ethereal solution of (±)-1a. Recrystallizations from methanol-ether and methanol gave white prisms, mp. 219-222°, lit.[4] mp. 234-235°. ^1H NMR (acetone-d_6/DMSO-d_6): δ 3.16 and 3.52 (2 s, 9H total, $\overset{+}{N}Me_3$), 3.63 (broadened d, J_{AB} = 12 Hz, 1H, H_A of $HOCH_CCH_AH_BN^+$), 3.88 (d of d, J_{BC} = 9 Hz, 1H, H_B), 6.1-6.25 (m, 2H, CH_COH), 7.5-7.7 (m, 3H), 7.83 (d, J = 6 Hz, 1H), 7.92 (d, J = 9 Hz, 1H), 7.98 (split d, 1H), 8.33 (d, J = 6 Hz, 1H).

Anal. Calcd for $C_{15}H_{20}INO$: C, 50.43; H, 5.64; N, 3.92; I, 35.53

Found: C, 50.27; H, 5.61; N, 4.01; I, 35.45

(-)-1-(1-Naphthyl)-2-dimethylaminoethanol Camphorsulfonate (8a).- A solution of equimolar amounts of racemic 1a (2.65 g.) and dry (+)-camphorsulfonic acid (2.86 g., mp. 198-201°, $[\alpha]_D^{21°}$ +33° (c 8.4, acetone))[11] in acetone was evaporated to dryness. The residual clear, colorless resin was recrystallized repeatedly from ethyl acetate (using somewhat more hot solvent than necessary to completely dissolve the crystals). Progress

of the resolution was followed via polarimetry on both the crystalline precipitates and the crystalline residues obtained from evaporation of the mother liquors. Residues from the sixth and seventh recrystallizations were collected, since they showed identical maximal negative rotations, $[\alpha]_D^{20.5^\circ}$ -18° (c 1.64, acetone), unchanged on further recrystallization. Recrystallization of (-)-8a from acetone-ethyl acetate gave white needles, mp. 136-137°.

Anal. Calcd for $C_{24}H_{33}NO_5S$: N, 3.13

Found: N, 3.13

(-)-1-(1-Naphthyl)-2-dimethylaminoethanol (1a).- Preceding (-)-camphorsulfonate salt was dissociated by shaking with ether and aqueous sodium hydroxide. The ether layer was washed with water and evaporated. The residue was treated with charcoal in acetone and recrystallized from ether to give (-)-1a as white prisms, mp. 66.5-70°, $[\alpha]_D^{22.5^\circ}$ $-158 \pm 3^\circ$ (c 0.61, $CHCl_3$).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51

Found: C, 78.01; H, 8.13; N, 6.73

(-)-1a Methiodide (7a).- Preceding (-)-hydroxyamine, (-)-1a, was dissolved in ether, treated with excess methyl iodide, and let stand for one hr. The precipitate was collected, washed with ether, and dried in vacuo to a white powder of (-)-7a, mp. 242.5-245°, $[\alpha]_D^{22.4^\circ}$ -77° (c 0.78, methanol). ^1H NMR (DMSO-d_6): δ 3.36 (s, $\overset{+}{N}Me_3$) which overlaps 3.44 (broadened d, J ≃ 15 Hz, 1H, H_A of $HOCH_CCH_AH_BN^+$), 3.72 (d of d, J_{AB} = 12 Hz, J_{BC} = 9 Hz, 1H, H_B), 5.96 (broad d, J = 12 Hz, 1H, H_C), 6.22 (d, J = 3 Hz, 1H, OH), 7.5-7.7 (3 overlapping t, 3H, H-3, H-6, H-7), 7.72, 7.92, 7.98, and 8.24 (4 d, J = 6-9 Hz, 4H, H-2, H-4, H-5, H-8).

Anal. Calcd for $C_{15}H_{20}INO$: C, 50.43; H, 5.64; N, 3.92; I, 35.53

Found: C, 50.12; H, 6.00; N, 3.97; I, 35.43

Acknowledgment.- This work was initiated by one of us (L.H.K.) while he was a Guggenheim Research Fellow at the Eidgenössische Technische Hochschule, Zürich, Switzerland, 1958-1959. It was completed recently at the University of Oregon.

REFERENCES

1. E. Campaigne, G. Skowronski and R. B. Rogers, Synth. Commun., 3, 325 (1973).

2. R. Howe, B. J. McLoughlin, B. S. Rao, L. H. Smith and M. S. Chodnekar, J. Med. Chem., 12, 452 (1969).

3. H. King and T. S. Work, J. Chem. Soc., 1307 (1940).

4. N. B. Chapman and D. J. Triggle, J. Chem. Soc., 4835 (1963).

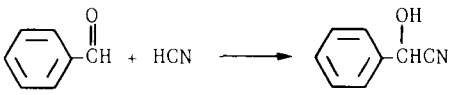
5. Since this step was improved markedly from the literature procedure[6] it is described in detail.

6. P. L. Southwick and L. L. Seivard, J. Am. Chem. Soc., 71, 2532 (1949).

7. Ethyl oxalyl chloride is now available from Aldrich Chemical Co.

8. F. F. Blicke and R. F. Feldkamp, J. Am. Chem. Soc., 66, 1087 (1944).

9. Preliminary studies indicate that (-)-7a can serve as an optical inducing agent for the reaction



10. V. M. Micovic and M. L. Mihailovic, J. Org. Chem., 18, 1190 (1953).

11. Houben-Weyl, "Methoden der Organischen Chemie," Vol. IV, Part 2, p. 514, Georg Thieme Verlag, Stuttgart, 1955.

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