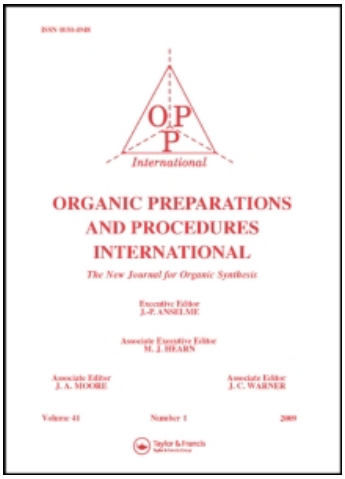

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AN IMPROVED SYNTHESIS OF (R)- AND (S)-2-METHYLPIPERAZINE

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OPPI BRIEFS

AN IMPROVED SYNTHESIS OF (R)- AND (S)-2-METHYLPIPERAZINE

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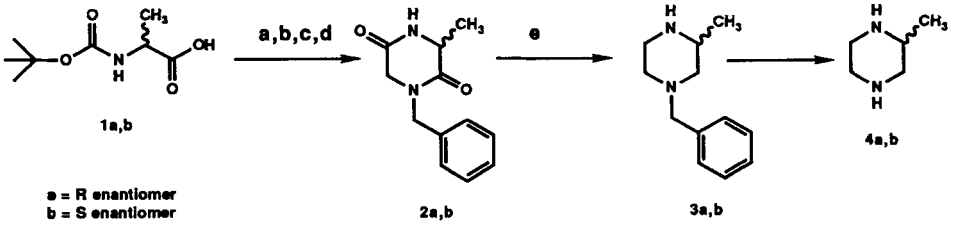
Multigram quantities of enantiomerically pure (R)-2-methylpiperazine (**4a**) and (S)-2-methylpiperazine (**4b**) were required for the preparation of certain quinolone antibacterials. No suitable procedure for the preparation of **4a** or **4b** could be located in the chemical literature. Although the procedure of Armarego [J. Chem. Res. (M), 1946 (1980)] suffers from low yield (18%), the concept utilized seemed to be potentially quite useful, except for the difficulty caused by the low solubility of the intermediate diketopiperazine in ether solvents suitable for hydride reductions. A logical extension of this work would be the incorporation of a nitrogen protecting group. The appropriate group would increase the solubility of the diketopiperazine, be inert to the carbonyl reduction conditions, and be easily removed without racemization after the reduction. The use of N-benzyl



a. dicyclohexylcarbodiimide, CH_2Cl_2, b. Ethyl N-benzyl glycinate, c. HCl gas, d. neutralization, e. $LiAlH_4$, THF, f. 20% Pd on Carbon, H_2, CH_3OH

was investigated and found to effectively solve the problems inherent in Armarego's procedure.

Standard peptide coupling of the enantiomeric N-Boc-alanines, **1a** and **1b** with ethyl N-benzylglycinate yielded the desired dipeptides. Without purification, these compounds were cyclized very efficiently through removal of the Boc group with HCl gas followed by neutralization to give the diketopiperazines, **2a** and **2b**. Reduction to the piperazines, **3a** and **3b**, was readily accomplished with lithium aluminum hydride in THF. No solubility problems were encountered even at 20-70 g scale. Catalytic removal of the N-benzyl group was also a straightforward procedure giving the desired 2-methylpiperazines, **4a** and **4b**, in excellent yields.

Because of the low specific optical rotation of **4a** and **4b**, we felt that measurement of opti-

cal rotation did not allow for the determination of optical purity with a sufficient degree of confidence. Therefore, an HPLC method based on the separation of diastereomeric derivatives was devised to determine the optical purity. This analysis was carried out on the N-benzyl-3-methylpiperazines, **3a** and **3b**, with the assumption that no racemization would occur in the debenzylation step.

EXPERIMENTAL SECTION

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined on a Nicolet FT IR SX-20 with 2 cm^{-1} resolution. ^1H NMR spectra were recorded on a Bruker AM-250 spectrometer. Chemical shifts are reported in δ relative to internal TMS. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with a 11/250 data system. All concentrations of solutions were performed under reduced pressure on a Buchi rotary evaporator. Elemental analyses were performed on a Control Equipment Corp. Model 240XA instrument. The Boc-D and L-alanines were obtained from Bachem, Inc.

(S)-(+)-3-Methyl-1-(phenylmethyl)-2,5-piperazinedione (**2b**).- Dicyclohexylcarbodiimide (81.0 g, 0.39 mol) was dissolved in CH_2Cl_2 (3000 mL) and cooled to <5°. To this solution was added N-Boc-D-alanine, (**1b**, 75.0 g, 0.39 mol) with stirring and the resulting slurry stirred for approximately 5 min. Ethyl N-benzylglycinate (76.5 g, 0.39 mol) was added and the suspension was stirred at ice bath temperature for 2 hrs, then allowed to warm and stir overnight. The reaction mixture was filtered to remove suspended dicyclohexylurea which was washed 2 x 100 mL with CH_2Cl_2. The combined CH_2Cl_2 was evaporated to a viscous oil which was dissolved in ether and allowed to stand at room temperature for several hours. The white solid that precipitated from solution was removed by filtration and the filtrate evaporated to an oil. This oil was redissolved in CH_2Cl_2 and HCl was bubbled through the solution with stirring until TLC analysis showed complete consumption of the initial dipeptide intermediate. The solvent was evaporated and the residue partitioned between ethyl acetate (approx. 2000 mL) and sufficient saturated $NaHCO_3$ solution to neutralize the HCl present. The ethyl acetate layer was washed with saturated NaCl solution, dried over $NaSO_4$, filtered and evaporated to a light yellow solid (110 g). This solid was crystallized from toluene to give the title compound as a colorless solid: 74.8 g (88%); mp. 137-139.5°; ^1H NMR ($CDCl_3$): δ 7.39-7.23 (m, 5H), 4.59 (s, 2H), 4.14 (q, 1H), 3.84 (s, 2H), 1.52 (d, 3H); mass spectrum, m/e 219 (M+1), 91, 44 base); $[\alpha]_D^{23}$ = +0.7° (c = 2.0, ethanol).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.84
Found: C, 65.69; H, 6.42; N, 12.68

(R)-(-)-3-Methyl-1-(phenylmethyl)-2,5-piperazinedione (**2a**).- The above procedure was repeated using N-Boc-D-alanine (**1a**) to give the title compound in 81% yield mp. 137-139.95°; ^1H NMR ($CDCl_3$): δ 7.39-7.23 (m, 5H), 4.59 (s, 2H), 4.14 (q, 1H), 3.84 (s, 2H),1.52 (d, 3H); mass spectrum, m/e 218 (M+), 91, 44 (base); $[\alpha]_D^{23}$ = -0.33° (c = 2.1, ethanol).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.84
Found: C, 65.98; H, 6.27, N, 12.61

(S)-(-)-3-Methyl-1-(phenylmethyl)piperazine (**3b**).- THF (2000 mL) was cooled to <5° and lithium

aluminum hydride (44.0 g, 1.16 mol) was added cautiously. Once all the hydride had been added the slurry was allowed to cool back to <5° and (S)-(-)-3-methyl-1-(phenylmethyl)-2,5-piperazinedione (**2b**, 70.0 g, 0.32 mol) was added. The cooling bath was removed and the mixture heated to reflux and maintained at reflux overnight. The reaction was cooled to <5° and 50 mL of water was cautiously added. This was followed by addition of 10% NaOH solution (50 mL) then water (50 mL) again. After stirring for 30 min., the white solid was removed by filtration and washed with THF. The combined THF solutions were evaporated and the residue distilled at 0.1 mm Hg at 92-95° to give **3b** as a light yellow low melting solid. The yield was 47.5 g (78%), mp. 30-33°; ^{1}H NMR ($CDCl_3$): δ 7.33-7.24 (m, 5H), 3.84 (s, 2H), 2.94-2.74 (m, 5H), 2.05-1.95 (m, 1H), 1.66 (apparent t, 1H), 1.00 (d, 3H, J = 6.2Hz); mass spectrum, m/e 190 (M+), 134 (base), 91, 44; $[\alpha]_D^{23}$= -8.2° (c = 2.0, chloroform).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.35; N, 14.72. Found: C, 75.27; H, 9.57; N, 14.71

(R)-(+)-3-Methyl-1-(phenylmethyl)piperazine (**3a**).- The above procedure was repeated using (R)-(+)-3-methyl-1-(phenylmethyl)-2,5-piperazinedione (**2a**) to give the title compound in 87% yield, mp. 29-32°; ^{1}H NMR ($CDCl_3$): δ 7.33-7.24 (m, 5H), 3.84 (s, 2H), 2.94-2.74 (m, 5H), 2.05-1.95 (m, 1H), 1.66 (apparent t, 1H), 1.00 (d, 3H, J = 6.2Hz); mass spectrum, m/e 190 (M+), 134 (base), 91, 44; $[\alpha]_D^{23}$ = +8.1° (c = 2.1, chloroform).

Anal. Calcd for $C_{12}H_{18}N_2 \cdot 0.09H_2O$: C, 75.10; H, 9.55; N, 14.60

Found: C, 75.12; H, 9.64; N, 14.28

HPLC analysis to determine the enantiomeric purity of **3a** and **3b** was performed as follows: a 4 mg sample was dissolved in CH_3CN (1 mL) and 1 drop of triethylamine and 8 mg of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate were added, the mixture was allowed to stand for 30 min. then was diluted with mobile phase (10 mL). Analysis was run on Supelco LC-18-DB column (5 μ, 250 mm x 4.6 mm) using 40% CH_3OH 60%/0.025 M $NH_4H_2PO_4$ / 0.5% triethylamine (pH = 2.5) at 1.5 mL/min as the mobile phase, with the detector wavelength at 250 nm. The R enantiomer (**3a**) and the S enantiomer (**3b**) had a retention time of 17.4 minutes and of 20.2 minutes respectively. Each was >99% pure.

(S)-(-)-2-Methylpiperazine (**4b**).- The (S)-(-)-3-methyl-1-(phenylmethyl)piperazine (5.39 g, 0.028 mol) was dissolved in methanol (100 mL) and 20% palladium on carbon (1.0 g) was added (Parr hydrogenator). The mixture was pressurized with hydrogen (50 psig) and shaken until the calculated hydrogen had been taken up. The reaction was depressurized and the catalyst removed by filtration. The collected catalyst was washed with methanol. The methanol (combined washings and original filtrate) was evaporated to give an oil. This oil was distilled (Kugelrohr) at 120 mm Hg (bp. 90-110°) to give a the title compound as a solid (2.13 g, 75%) mp. 85-87°, a mixed melting point with **4a** gave mp. 63-65°, $[\alpha]_D^{23}$= -5.6° (c = 1.0, 2N HCl); ^{1}H NMR ($CDCl_3$): δ 3.00-2.64 (m, 6H), 2.35 (dd, 1H, J = 9.9, 12Hz), 1.95 (s, 2H), 1.01 (d, 3H, J = 6.2Hz); mass spectrum, m/e (M+), 84, 56, 49 (base).

Anal. Calcd for $C_5H_{12}N_2 \cdot 0.12CH_3OH$: C, 59.23; H, 12.09; N, 26.93

Found: C, 59.23; H, 11.78; N, 26.88

(R)-(+)-2-Methylpiperazine (**4a**).- The above procedure was repeated using (R)-(+)-3-methyl-1-(phenylmethyl)piperazine to give **4a** in 85.5%, mp. 81-84°, $[\alpha]_D^{23}$ = +4.9° (c = 1.0, 2N HCl).
Anal. Calcd for $C_5H_{12}N_2 \cdot 0.14CH_3OH$: C, 58.99; H, 12.10; N, 26.77
Found: C, 58.71; H, 11.98; N, 26.82

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TRANSFORMATION OF SOME β-TETRALONES TO 1,3-DIFORMYL-2-CHLORONAPTHALENES

Submitted by (04/19/90) S. L. Evans*†, H. A. Lloyd††, D. LeBeau† and E. B. Sokoloski††

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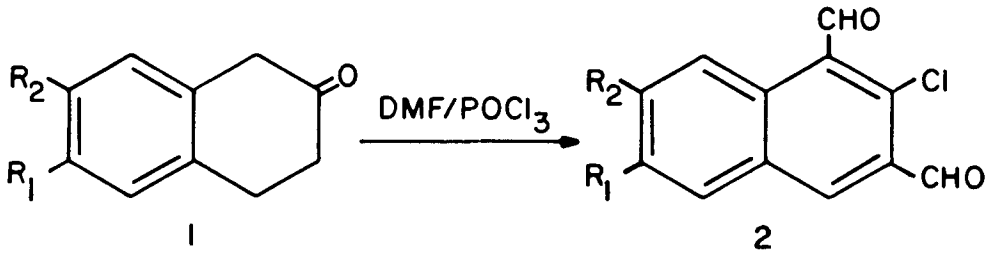
The Vilsmeier reagent is capable of formylating activated aromatic rings,[1] converting aryl benzyl ketones into β-chlorovinyl aldehydes[2] and transforming aryl ketones to aryl dichloroindenes.[2] We now report the formylation and aromatization of a series of β-tetralones under mild conditions by dimethylformamide (DMF) and phosphorous oxychloride ($POCl_3$).



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a) $R_1 = R_2 = H$ b) $R_1 = R_2 = OCH_3$

We found that β-tetralones are converted to their corresponding diformyl naphthalenoid derivatives with DMF-$POCl_3$. Katritzky et al.[3] reported the diformyl aromatization of a series of 2-cyclohexen-1-ones under Vilsmeier reaction conditions and offered a plausible mechanism for the diformyl benzenoid derivatives formed. Paquette[4] reported monoformylation without aromatization with β-tetralone under Vilsmeier conditions. Both the molar ratio of Vilsmeier reagent to starting ketone and the reaction time were greater in our reaction procedure than in the preceding examples. This may serve as a rationale for the difference in the products obtained. α-Tetralone and 6-methoxy-1-tetralone yield the corresponding monoformyl derivatives (1-chloro-3,4-dihydro-2-naphthaldehyde and 6-methoxyl-1-chloro-3,4-dihydro-2-naphthaldehyde) without aromatization