several days. The dimer **9**—separated by filtration—is not pure (contains trace amounts of the "glassy" blue monomer). On heating, the crude dimer **9** turns into the "glassy" deep blue monomer at 125–137 °C. The IR spectrum of the colorless crude dimer **9** is quite similar to that of the monomer **8**, and its methyl group gives a singlet at δ 2.40 (downfield from Me_4Si) in the ^1H NMR spectrum.

Deoxygenation of 2,3-Diphenylthiirene 1-Oxide (2a) with Hexachlorodisilane (10). The sulfoxide **2a** (0.155 g, 0.685 mmol) and the deoxygenation agent **10** (0.1882 g, 0.7 mmol) were mixed together in dry CH_2Cl_2 (5 mL) for 1 h. Workup according to the procedure of Mislow et al.[19] afforded diphenylacetylene in essentially quantitative yield (0.125 g). The spectrophotometric data of the product were identical with those of an authentic sample.

Reaction of Thiirene 1-Oxide 2a with Diiron Nonacarbonyl: Synthesis of the Organosulfur–Iron Complex (μ,μ'-(*cis*-Stilbene-α,β-dithiolato))bis(tricarbonyliron) (15). 2,3-Diphenylthiirene 1-oxide (**2a**) (1.215 g, 5.37 mmol) and diiron nonacarbonyl (1.953 g, 5.37 mmol) were stirred in anhydrous ether (150 mL) at room temperature over a period of 4 h. The dark red etheral solution was filtered through a Celite filter aid (to remove unreacted iron carbonyls), and then it was chromatographed on a column packed with silica gel to yield 0.969 g (34.6%) of a red viscuous oil. A second chromatography using benzene as an eluant afforded the pure complex **15** (0.785 g, 28%) as a viscous dark red oil which solidified in the refrigerator (no optimization of the yield was attempted). The spectral data and the elemental analysis of the product **15** were in full agreement with that of the known **15**,[25] including the single-crystal X-ray analysis:[26] ^{13}NMR δ 207.8 (CO), 131.7–123.4 (C Ar), 89.4 (C=C).

Acknowledgment. This research was supported by a grant from the United States–Israel Binational Science Foundation (BSF), Jerusalem, Israel, and is gratefully acknowledged. Also, the author wishes to thank the NIH for support.

Registry No. **2a**, 31247-21-9; **5**, 4083-64-1; **8**, 94731-68-7; **9**, 94731-69-8; **10**, 13465-77-5; **15**, 14406-62-3; diphenylacetylene, 501-65-5; diiron nonacarbonyl, 15321-51-4.

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Chiral Synthesis of Doxpicomine

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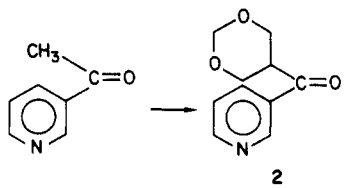
The syntheses and novel analgesic activities of a variety of 1,3-dioxanylamines were described by Booher.[1] One compound from this group, (*R*)-α-(1,3-dioxan-5-yl)-*N*,*N*-dimethyl-3-pyridinemethanamine hydrochloride (**1**),[2] was selected for further biological study. Recently, the analgesic activity of **1**, doxpicomine, in humans was reported.[3] In support of such studies, a more efficient synthesis of this compound was needed.

While examining other approaches to doxpicomine a procedure was devised to prepare conveniently the 1,3-dioxan-5-yl 3-pyridyl ketone (**2**) in one step in 57% yield by condensation of 3-acetylpyridine with paraformaldehyde and boron trifluoride etherate in acetic acid.



2

Various routes were examined to utilize this ketone in a chiral synthesis. The successful route followed the work of Nichols,[4] who reduced imines prepared from (S)-(−)-α-methylbenzylamine and various phenylacetones. A similar procedure was also used by Pirkle[5] for the synthesis of (*S*)-(+)-2,2,2-trifluoro-1-phenylethylamine. The route devised is depicted in Scheme I.

The ketone **2** reacted sluggishly with (*S*)-(−)-α-methylbenzylamine in the preparation of the imine. With acid catalyst in a hydrocarbon solvent with removal of water, yields of 70% were obtained. Yields of greater than 90% were obtained by using titanium tetrachloride[6] in methylene chloride. Slightly more than 1 equiv of the α-methylbenzylamine was used and 6 equiv of triethylamine were added as the acid scavenger.

Although the imine was not crystalline and could not be purified, spectral data confirmed its structural assignment as **3**. Both the ^{13}C and ^{1}H NMR spectra indicate that the imine is present principally as a single geometric isomer. Comparison of the ^{13}C spectrum of the imine with that of the ketone as described by Bunnell and Fuchs[7] shows an upfield shift of the 2 and 4 carbons of the pyridine ring of 7.14 and 1.71 ppm. The carbons of the dioxane portion show only a small downfield shift. Thus the pyridyl and α-methylbenzylamine groups are assigned syn geometry. In a recent report[8] a 4:1 ratio of *E* and *Z* isomers was found for the imine base prepared from 2-norbornanone and (*R*)-α-methylbenzylamine.

Initially, catalytic hydrogenation was used in reduction studies and the product was evaluated by HPLC.[9] Using 10% Pd–C, modest diastereomeric selection was found at room temperature: 72% of the desired ***R*,*S*** diastereomer and 28% of the *S*,*S* diastereomer (44% de). Hydrogenation at 0–5 °C gave only a slight improvement in this ratio (56% de). Nichols[4] found high diastereoselection in his series of compounds using these conditions. Reduction with sodium cyanoborohydride and acid gave similar results, 50% de, with **3**. Again these conditions were similar to those of Pirkle where reduction of some fluoroalkylated imines gave good diastereoselection.

Surprisingly, the diastereoselection on reduction of **3** was markedly improved by using sodium borohydride in methanol. With 1 molar equiv of borohydride at room temperature an 80% de was obtained. The best diastereoselection was found at −45 to −40 °C where 88% de was obtained routinely.

The diastereomeric ratio obtained reflects the presence of a single geometric isomer as seen by ^{13}C NMR. The product obtained is best explained by the Felken[10] model

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(9) High-performance liquid chromatography (HPLC) analyses were performed with Water Associates components including a M-45 pump, a Model U61K injector, a Model 440 detector, and an RCM-100 module with a RPCN column. The *R*,*S* and *S*,*S* diastereomers were separated with base-line resolution using 90% H_2O:10% CH_3CN:1% 5 M dibutyl ammonium phosphate buffer as solvent.

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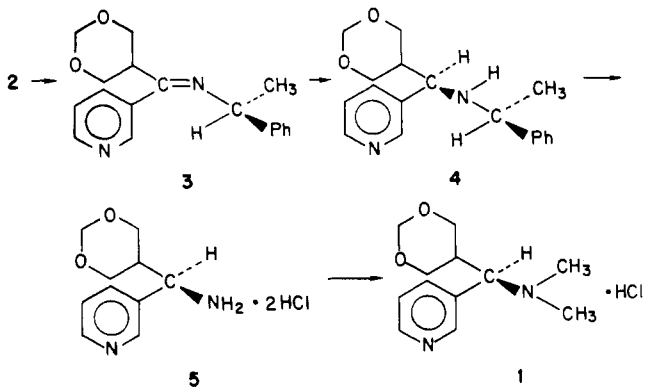
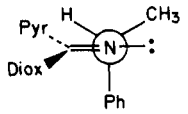
Scheme I



transition state shown with hydride approaching the carbon of the imine from the top yielding the *R* product at carbon.



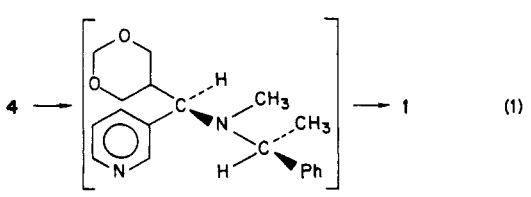
The presence of amino groups and their likely complexation with borohydride may alter this interpretation. The diastereomeric product obtained was of sufficient optical purity to be used to complete the synthesis of the target amine **1**. In addition, the desired pure *R,S* diastereomer was isolated at this point as either the free base or the monohydrochloride. The former was obtained optically pure in 55% yield. Optically pure *R,S* hydrochloride was also prepared from the diastereomeric mixture in 65% yield.

The debenzylation step also presented some difficulties. Attempts to effect catalytic hydrogenolysis of the benzylamine **4** using 10% Pd–C with the free base monohydrochloride, or dihydrochloride (the latter two compounds prepared in situ), failed. Only traces of the desired primary amine were found by TLC assay.

Thus, catalytic hydrogen transfer[11] was studied. With cyclohexene and 10% Pd–C catalyst in ethanol, the debenzylations of the free base, monohydrochloride, and dihydrochloride were attempted. Best results were obtained by using the dihydrochloride, again prepared in situ, where yields of about 90% of the primary amine dihydrochloride **5** were obtained. No evidence of any appreciable hydrogenolysis of the pyridylmethine bond was found.

The dimethylamine was prepared by methylation using the Eschweiler–Clarke[12] procedure. No apparent racemization occurred during this reaction. The monohydrochloride was then prepared to obtain the target amine **1**. Assay of the free base by NMR with a chiral shift reagent showed the presence of a single enantiomer.

During the course of these studies, formic acid was examined in debenzylation attempts. These studies led to an improved synthesis of **1** as shown in eq 1. Thus the



(1)

debenzylation and dimethylation reactions were carried out in a single step by slight modification of the Eschweiler–Clarke conditions used above. A larger ratio of formic acid was needed to obtain the best yields. The NCH_3 compound with the 2-methylbenzylamine moiety still attached appears to be an intermediate in this reaction as seen by TLC, MS, and NMR analyses. A new three-proton singlet is seen at δ 1.94 in the NMR, and MS shows m/e 312 (M^+) for this intermediate. With use of this modification for the synthesis of **1**, the overall yield is comparable to the previous route; however, one step is eliminated. Again, no racemization was observed during this reaction.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were run on a Beckman AccuLab 4 spectrometer in $CHCl_3$. NMR spectra were obtained with Varian EM360L, Brucker WM270, Brucker WH360, and Brucker WM250 (^{13}C) spectrometers in $CDCl_3$ solution except where designated otherwise. Mass spectra were obtained with a Varian MAT-371 instrument and optical rotations were obtained with a Perkin-Elmer 241 instrument. TLC was done with 0.25-nm silica gel $60F_{254}$ (Merck) glass plates.

1,3-Dioxan-5-yl 3-Pyridyl Ketone (2). In a 1-L, three-necked round-bottomed flask equipped with a mechanical stirrer, dropping funnel, condenser, and thermometer was placed 60.5 g (0.5 mol) of 3-acetylpyridine, 250 mL of acetic acid, and 54 g (1.8 mol) of paraformaldehyde. After the reaction mixture was cooled in an ice bath, 184.5 mL (1.5 mol) of boron trifluoride etherate was added dropwise with stirring. The reaction mixture was then stirred at about 65 °C for $2^1/_2$ h. After the reaction mixture was cooled to 25 °C, the pH was adjusted to 7.5–8 with ammonium hydroxide. The resulting mixture was extracted with methylene chloride (3 × 200 mL). The combined organic layer was washed with brine, dried, and evaporated. The residue was crystallized from isopropyl alcohol to give 54.4 g: mp 98–100 °C; ^1H NMR δ 89.2 (m, 1 H), 8.84 (m, 1 H), 8.12 (m, 1 H), 7.33 (m, 1 H), 4.85 (q, 2 H), 4.11 (br m, 5 H).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25; O, 24.84. Found: C, 62.02; H, 5.92; N, 6.91; O, 25.14.

(*S*)-(−)-*N*-[(1,3-Dioxan-5-yl)(3-pyridyl)methylene]-α-methylbenzylamine (3). To a 2-L round-bottomed flask equipped with stirrer and dropping funnel were added 38.6 g (0.2 mol) of ketone **2**, 463 mL of methylene chloride, 30 mL (0.236 mol) of *l*-(−)-α-methylbenzylamine, and 167 mL (1.2 mol) of triethylamine. The solution was cooled in an ice bath and a solution of 77 mL of methylene chloride and 15.4 mL (0.14 mol) of titanium tetrachloride was added dropwise with stirring. Upon completion of the addition, the reaction mixture was stirred at room temperature for 5.5 h and 5 mL of water was added dropwise. This resulted in a thick reaction mixture that became fluid after a few minutes of stirring. More water, 15 mL, was added and 10 g of Hyflow. After a few minutes of stirring, the mixture was filtered and the cake was washed with 4 × 100 mL of methylene chloride. The solvent was removed from the filtrate, leaving a yellowish viscous oil: 55.5 g; IR 1640 cm^{-1}; ^2H NMR δ 8.65 (m, 1 H), 8.31 (s, 1 H), 7.38–7.19 (m, 7 H), 5.01 and 4.65 (2 d, 2 H), 4.33 (m, 1 H), 4.28 (m, 1 H), 4.12 (m, 1 H), 3.91 (m, 1 H), 3.11 (m, 1 H), 1.34 (d, 3 H); MS, m/e 296 (M^+).

(*R,S*)-α-(1,3-Dioxan-5-yl)-*N*-(1-phenylethyl)-3-pyridinemethanamine (4). In a round-bottomed flask was placed 46 g (0.155 mol) of **3** and 725 mL of methanol. This solution with stirring was cooled to about −40 °C and 5.87 g (0.155 mol) of sodium borohydride was added. The solution was stirred at about −40 °C for 6.5 h. At this point, an aliquot was removed for HPLC analysis which showed the presence of 94.2% *R,S* and 5.8% *S,S* diastereomers. Thus 120 mL of acetone was added and the solution was warmed to room temperature. After the volume was reduced to one-half in vacuo, excess 20% sodium chloride solution was added. This solution was extracted with 4 × 150 mL of methylene chloride. The latter combined solution was washed with brine and dried, and the solvent was evaporated to give 46.1 g of oil which crystallized on standing.

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An aliquot, 3.0 g, of the oil was dissolved in 25 mL of ethyl ether, filtered, and concentrated to 12 mL. This solution was stirred while cooling at about -20 °C for crystallization. Filtration gave 1.86 g: mp 89-92 °C; ^{13}C NMR δ 149.18, 148.96, 145.75, 137.13, 134.50, 128.39 (2C), 127.09, 126.54 (2C), 123.67, 94.17, 69.03, 57.06, 55.07, 41.02, 22.18.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.18; H, 7.34; N, 9.19.

The hydrochloride was prepared by dissolving some of the oil in acetone and adding an equivalent of hydrochloric acid in acetone with stirring at room temperature and then cooling with stirring at about -20 °C. The crystals were filtered and dried: mp 196-199 °C; α^{25}_{365} -41.0° (c 1, H_2O). HPLC analysis confirmed this to be the pure *R,S* diastereomer.

Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 64.57; H, 6.92; N, 8.37; Cl, 10.59. Found: C, 64.63; H, 7.00; N, 8.17; Cl, 10.58.

(*R*)-α-(1,3-Dioxan-5-yl)-3-pyridinemethanamine Dihydrochloride (5). To a round-bottomed flask was added 4.44 g (0.0149 mol) of **4**, 98 mL of ethanol, and 80 mL of cyclohexene. After cooling in an ice bath, 2.48 mL of hydrochloric acid and a slurry of 1.33 g of 10% Pd-C in 16.25 mL of water were added. With stirring, the mixture was heated at reflux for 20 h. The reaction mixture was filtered while hot and the catalyst was washed with hot ethanol. The filtrate was concentrated to about one-half volume and cooled to give 3.13 g of **5**; mp 232-236 °C dec. Further concentration gave an additional 0.35 g; mp 230-232 °C dec; ^1H NMR (H_2O) δ 9.01 (s, 1 H), 8.93 (d, 1 H), 8.78 (d, 1 H), 8.25 (m, 1 H), 5.12 (d, 1 H), 4.98 (d, 1 H), 4.88 (d, 1 H), 4.23 (m, 1 H), 4.17 (m, 1 H), 3.89 (m, 1 H), 3.62 (m, 1 H), 2.49 (m, 1 H). Anal. Calcd for $C_{10}H_{16}N_2O_2Cl_2$: C, 44.96; H, 6.04; N, 10.49; Cl, 26.54. Found: C, 44.72; H, 6.04; N, 10.76; Cl, 26.76.

(R)-(-)-α-(1,3-Dioxan-5-yl)-*N*,*N*-dimethyl-3-pyridinemethanamine Hydrochloride (1). In a round-bottomed flask was placed 3.55 g (0.0133 mol) of the dihydrochloride **5**, 25 mL of methanol, 5 mL of water, and 2.5 mL of ammonium hydroxide. Upon solution, the volatile solvents were removed under vacuum. To the residue was added 30 mL of formalin (37%) and 30 mL of formic acid. The solution was heated on a steambath for 18 h. Most of the volatile solvents were removed under vacuum and excess water and methylene chloride were added. Then 10% potassium carbonate solution was added with stirring until pH ~9. This mixture was extracted with 3 × 100 mL of methylene chloride. The combined organic layers were washed with brine, dried, and evaporated, giving 2.65 g of an oil. The NMR spectrum of this oil was identical with a previous sample.[1] The monohydrochloride was prepared by dissolving the oil in 100 mL of acetone, and with stirring a solution of 0.99 mL (0.12 mol) of hydrochloric acid in 20 mL of acetone was added dropwise. The crystals were filtered and washed with cold acetone to give 2.7 g, mp 229-232 °C dec. After recrystallization from ethanol there was obtained 2.3 g: mp 234-236 °C dec; α^{25}_{365} -16.7° (c 1, H_2O).

The free base was liberated from a sample and the NMR was run with a chiral shift reagent, $Eu(tfc)_3$, added. The six-proton *N*-dimethyl singlet showed no evidence of the *S* enantiomer. This assay was found to detect the other enantiomer at the 1% level.

Debenzylation-Dimethylation to 1. To a round-bottomed flask were added 13.4 g (0.045 mol) of **4**, 98 mL of formic acid (90%), and 42 mL of formalin. The solution was heated at reflux for 24 h. The solution was cooled to room temperature and 80 mL of water was added. This mixture was extracted with 3 × 25 mL of chloroform, and the wash was discarded. To the aqueous solution was added sufficient ammonium hydroxide with cooling to adjust the pH to 9. This solution was extracted with 3 × 60 mL of methylene chloride. The organic solution was washed with brine, dried, and evaporated, leaving 8.15 g of an oil. Both TLC and NMR showed good agreement with the free base of 1.

This oil was dissolved in 85 mL of acetone, and with stirring a solution of 3.1 mL of hydrochloric acid in 15 mL of acetone was added. This mixture was stirred at room temperature for 0.5 h and in an ice bath for 1 h. The mixture was filtered and the crystals were dried to give 8.5 g: mp 223-226.5 °C dec. Recrystallization from ethanol gave 6.6 g: mp 236-238 °C dec; α^{D}_{365} -16.6° (c, 1, H_2O).

Acknowledgment. We acknowledge the contributions of our colleagues in microanalysis and physical chemistry who obtained the data used in this paper. The assistance of Mr. J. W. Paschal in the generation and interpretation of some of the NMR data was especially valuable.

Registry No. 1·HCl, 69494-04-8; **1**, 62904-71-6; **2**, 85727-04-4; **3**, 94844-55-0; **4**, 94844-56-1; **4**·HCl, 94844-57-2; **4** *S,S* isomer, 94844-58-3; **5**, 94903-53-4; 3-acetylpyridine, 350-03-8; paraformaldehyde, 30525-89-4; *l*-(-)-α-methylbenzylamine, 2627-86-3.

A Simple and Convenient Method for the Preparation of Ketomethylene Peptide Analogues

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Ketomethylene peptide analogues are peptide isosteres in which the -NH- group of a particular amide bond has been replaced by a methylene group. Unlike a peptide bond, the ketomethylene group is stable to enzyme-catalyzed hydrolysis, thus giving these molecules great potential as probes of protease enzyme mechanisms and active-site interactions. Ketomethylene analogues are finding increasing use both in this area[1-4] and in clinical applications.[5-8] In the course of our studies of ketomethylene compounds as serine protease inhibitors, to be reported elsewhere, we have synthesized a series of methyl 3-peptidylpropionates (ketomethyleneglycine analogues) and peptidylmethanes (peptide methyl ketones) (Table I). We describe here a simple, general procedure for the preparation of ketomethylene analogues in which protected peptides can be converted directly to carboxy terminal ketones.

Our new synthesis of ketomethylene analogues is based on a modification of the Dakin-West reaction[9] developed by Steglich and co-workers.[10-12] The precursor, a suitably protected N^{α}-acyl amino acid, dipeptide, or tripeptide (or presumably a larger peptide if desired) possessing a free terminal carboxyl function, is heated at 40-50 °C with triethylamine (Et_3N), 4-(dimethylamino)pyridine (DMAP), and the appropriate acid anhydride. Peptidylpropionates are prepared by using the symmetric anhydride of monomethyl succinate (MMS) (**10a**) whereas the corresponding methyl ketones are prepared by using acetic anhydride (**10b**). The benzyloxycarbonyl (Z) side-chain protection of lysine and the α-*tert*-butyloxycarbonyl (Boc) protecting

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