The Resolution of an Optically Active Pyridinethiol

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The resolution of a chiral pyridine thiol has been conveniently carried out through derivatives with optically active α-phenethylisocyanates. Optically active heterocyclic thiols in which the thiol occupies the center of chirality are not known in the literature. In conjunction with a synthetic program dealing with derivatives and analogues of 5-mercaptopyridoxine (1), the preparation of such species was accomplished. Their resolution proved to be difficult, but the techniques devised herein should prove of general utility for other heterocyclic thiols or alcohols.

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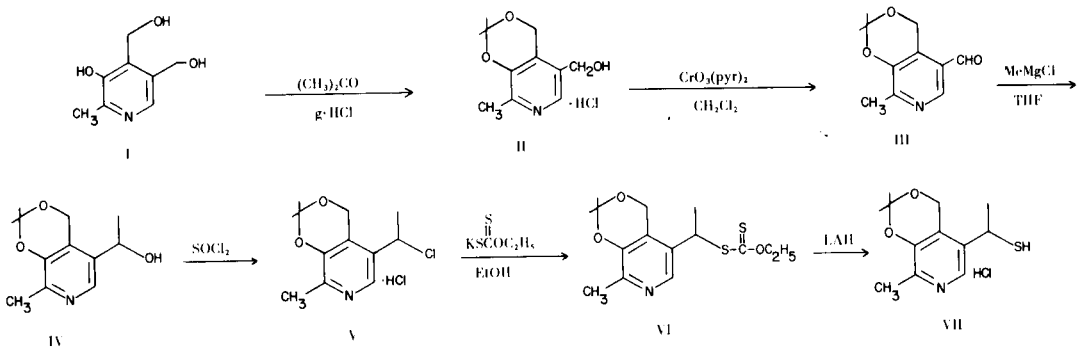
Pyridoxine hydrochloride was converted to its 3,4α-di-*O*-isopropylidene derivative II by the procedure of Korytnyk and co-workers (2). Carbinol II was in turn oxidized to the corresponding aldehyde III in good yield with chromium trioxide/pyridine in methylene chloride (3). The crystalline aldehyde reacted cleanly with methyl magnesium chloride (4) to give secondary alcohol IV. This was converted *via* its chloride hydrochloride V to its ethyl xanthate ester VI. Several techniques can be used to convert ester VI to racemic thiol VII. It was generally observed that hydrolytic methods tended to give troublesome amounts of the corresponding alcohol and disulfide, though this latter impurity could be minimized by scrupulous exclusion of air. Most preferable was the liberation of the thiol with lithium aluminum hydride at 25°. These transformations are summarized in Scheme I.

Several direct resolutions of this thiol were attempted with a variety of optically active acids. The salts obtained were so poorly crystalline that attempts at recrystallization led invariably to oils.

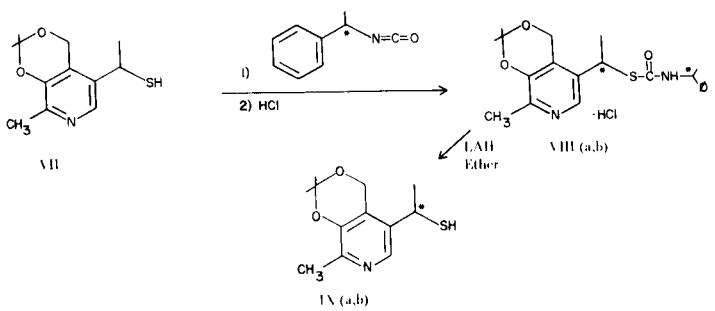
Efforts were then directed toward making a diastereoisomic reaction product of the mercaptan. Of several derivatives, the thiourethanes from optically active α-phenethylisocyanate proved to be the keys to success (both enantiomers are commercially available) (5). Although the thiourethanes themselves were very low melting, their corresponding hydrochlorides were highly crystalline and stable. These hydrochlorides were recrystallized to constant melting point and constant rotations.

These thiourethanes were then converted to the free thiols with lithium aluminum hydride at 25° in tetrahydrofuran. After deblocking, both enantiomers were found to have rotations of equal magnitude but opposite sign. Control experiments demonstrated that no apparent racemization occurred under deblocking conditions. These

Scheme I



Scheme II



transformations are depicted in Scheme II.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infrared Model 137. Rotations were measured on a Perkin-Elmer Model 141 polarimeter. All rotation values refer to a 1 decimeter cell. Nmr spectra were determined on a Varian Model A-60A.

2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine-5-methanol (II) (2).

A 12 liter 4-necked flask was fitted with a stirrer, drying tube, thermometer, and gas inlet tube. To this was charged anhydrous acetone (5.5 l.) and cooled to -20°. The solution was saturated with dry hydrogen chloride at -20°. Then pyridoxine hydrochloride (800 g., 3.9 moles) was added with continual passage of hydrogen chloride, a clear solution was obtained. The hydrogen chloride addition was stopped and 5 l. of diethyl ether was introduced over .5 hour. The resulting precipitate was aged at -10-15° for .5 hour and isolated by filtration. It was washed with a 1:1 acetone ether mixture (1 l.), followed by ether (3 x 400 ml.). The precipitate was dried by pulling nitrogen through it until constant weight was attained. Yield 877 g. (91.8%), m.p. 210-211° [lit. (2) 209-211°].

The free base was obtained by treating the hydrochloride with excess aqueous bicarbonate solution, followed by isolation by filtration and washing with water.

2,2,8-Triemtheyl-4*H*-*m*-dioxino[4,5-*c*]pyridine-5-carbaldehyde (III).

Chromium trioxide (750 g., 1.24 moles) was added in portions to a stirred mixture of pyridine (1186.5 g., 15 moles) in methylene chloride (3.75 l.) at room temperature. An ice bath was necessary to maintain 25° ± 2°. After addition was complete, the solution was aged .5 hour at 10-15°. Then the free base II (304 g., 1.24 moles) was added in portions with good stirring. After this addition was complete, the reaction was aged at room temperature for 1 hour, then for 1 hour at 40°. The reaction was cooled to room temperature and filtered through super-cel. The black tarry residue was triturated with methylene chloride (4 x 250 ml.). The combined methylene chloride phases were washed with 5% sodium hydroxide (1 x 400 ml.), once with saturated sodium chloride solution (400 ml.), and was then dried over anhydrous magnesium sulfate. After concentration *in vacuo*, a viscous oil was obtained which was azeotroped with toluene (2 x 300 ml.). Pumping *in vacuo* resulted in crystallization to a dark brown solid, 151.4 g. (59%) m.p. 56-60°.

1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-5-yl)ethanol (IV).

A solution of aldehyde III (20.7 g., 0.1 mole) in tetrahydrofuran (180 ml.) was added dropwise with stirring under nitrogen to 3.6 *N* methylmagnesium chloride (4) in tetrahydrofuran (45 ml.). Cooling was necessary to maintain the temperature between 25-30°. After aging 3 hours at room temperature, the reaction was quenched on a mixture of ice water (200 g.) ammonium chloride (30 g., 0.57 mole) and ether (400 ml.). After stirring well for 15 minutes, the ether layer was separated, dried over magnesium sulfate, and evaporated *in vacuo* to afford 18.5 g. (83%) of off-white crystalline carbinol, m.p. 120-121°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.68; N, 6.27. Found: C, 64.66; H, 7.45; N, 6.43.

1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-5-yl)ethyl Chloride Hydrochloride (V).

A mixture of carbinol IV (38.0 g., 0.17 mole) thionyl chloride (21.8 g., 0.2 mole), and benzene (425 ml.) was refluxed with stirring for 2 hours. The reaction mixture was then cooled and evaporated *in vacuo* leaving a tacky solid. This was triturated with ether (120 ml.) and the precipitate isolated by filtration and washed with fresh ether (75 ml.). After drying *in vacuo*, 45 g. (95%) of a grey solid was obtained, m.p. dec., >220°.

Anal. Calcd. for $C_{12}H_{17}Cl_2NO_2$: C, 51.80; H, 6.17; N, 5.03. Found: C, 51.87; H, 6.19; N, 4.95.

Ethyl 1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-5-yl)ethyl Xanthogenate (VI).

A solution of compound V (16.38 g., 0.058 mole) in ethanol (400 ml.) was added dropwise with stirring under argon at 0-5° to a solution of potassium ethyl xanthate (38.0 g., 0.23 mole) in distilled water (300 ml.). The mixture was left for 1 hour at 0.5° followed by 16 hours at room temperature. The mixture was quenched on ice water (600 ml.) and extracted with ether (3 x 400 ml.). After drying over magnesium sulfate, evaporation *in vacuo* left a light brown oil, 18.3 g. (96%) of crude xanthate. An analytical sample was obtained by chromatography on silica gel G (eluent 95:5 chloroform:methanol).

Anal. Calcd. for $C_{15}H_{21}NS_2O_3$: C, 55.03; H, 6.46; N, 4.28; S, 19.56. Found: C, 55.13; H, 6.40; N, 4.35; S, 19.61.

For synthetic purposes, the crude ester was perfectly adequate as prepared without further purification.

1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-5-yl)ethanethiol (VII).

A solution of crude xanthate VI (18.3 g., 0.056 mole) in anhydrous ether (150 ml.) was added dropwise with stirring under argon to a suspension of lithium aluminum hydride (3.0 g., 0.078 mole) in ether (150 ml.) at -20°. The reaction was left for 2 hours at -10-20° and was then quenched on ice water (500 ml.) containing ammonium chloride (30 g., 0.57 mole). An atmosphere of argon was maintained during the quench. After aging for 15 minutes, the ether layer was separated, dried over magnesium sulfate, and concentrated *in vacuo* to yield 12.3 g. of a tan oil (92%). This oil was dissolved in tetrahydrofuran (40 ml.) and saturated with hydrogen chloride at 5°. The resulting crystalline precipitate was isolated, washed with 25 ml. of ether, and dried *in vacuo* to afford 13.16 g. (100%) of pure hydrochloride.

Anal. Calcd. for $C_{12}H_{18}ClNSO_2$: C, 52.26; H, 6.58; N, 5.08; S, 11.63. Found: C, 52.15; H, 6.78; N, 4.93; S, 11.58.

[1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridinyl)ethyl]-*N*[α-phenethyl]thiolcarbamate (VIII) (**a,b**) (5).

A mixture of thiol VII (2.39 g., 0.01 mole) plus (-)-α-phenethylisocyanate (α_D-89.3°) (1.55 g., 0.005 mole) in anhydrous ether (25 ml.) was stirred for 8 hours. The soluiton was concentrated *in vacuo* and the residue taken up in tetrahydrofuran (40 ml.). This solution was cooled to 0° and saturated with dry hydrogen chloride. This soluiton was concentrated *in vacuo* and the residue recrystallized six times from absolute ethanol until crystals of VIII having a constant melting point and rotation were obtained. The (-)-thiourethane hydrochloride VIIIa (1.6 g.) isolated in this fashion melted at 241-241.5° dec. eff., (α_D-108.9°) (C = 41.8 mg./10 ml., DMF/methanol: 4/1).

The residual first two mother liquors from the above crystallizations were combined and seeded with pure crystalline VIIIa. Crude solid was filtered off over two days. After this time the solution was evaporated to dryness and dissolved in fresh tetrahydrofuran. Overnight crude crystals of a (-)-thiourethane hydrochloride m.p. 180-220° dec. eff., (α_D = -46°) came out (0.72 g.). This material was repeatedly recrystallized from tetra-

hydrofuran to reach a terminal m.p. 165-176° and optical rotation (α_D = -76°) (C = 25 mg./10 ml., DMF/methanol: 4/1) VIIIb (0.11 g.).

Anal. Calcd. for $C_{21}H_{27}ClN_2SO_3$: C, 59.63; H, 6.43; N; 6.62; S, 7.58. Found: C, 59.75; H, 6.61; N, 6.50; S. 7.75.

(-)-1(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-5-yl)ethanethiol (IXa).

A solution of VIIIa (1.0 g., 0.00236 mole, α_D = -108.9°) in methanol (50 ml.) was treated with excess triethylamine and the solution concentrated *in vacuo*. The residue was partitioned between ethyl acetate (25 ml.) and distilled water (25 ml.). The ethyl acetate layer was dried over magnesium sulfate and concentrated *in vacuo* to a yellow oil. This oil was dissolved in anhydrous tetrahydrofuran (25 ml.) and added dropwise with stirring under argon to a suspension of 0.65 g. (0.017 mole) lithium aluminum hydride (0.65 g., 0.017 mole) anhydrous ether (50 ml.) at room temperature. The reaction was left 30 minutes at room temperature and was then cooled to -50°. A solution of water (20 ml.) in tetrahydrofuran (20 ml.) was added, followed by a mixture of ethyl acetate (100 ml.) and a solution of ammonium chloride (10.0 g.) in water (40 ml.). After shaking well, the organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo* to a yellow oil, IXa, 0.51 g. (90.5%) [α_D = -33.1° ± 0.5°] (C = 40.0 mg./4 ml. methanol).

Anal. Calcd. for $C_{12}H_{17}NSO_2$: C, 60.23; H, 7.15; N, 5.85; S, 13.38. Found: C, 60.40; H, 7.01; N, 5.77; S, 13.35.

(+)-1-(2,2,8-Trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridin-4-yl)ethanethiol (IXb).

A sample of VIIIb (1.5 g., 0.0035 mole) was converted to its free base as with VIIIa. This was dissolved in anhydrous tetrahydrofuran (40 ml.) and added dropwise with stirring to a suspension of lithium aluminum hydride (1.0 g., 0.026 mole) in ether (50 ml.). The reaction mixture was left 30 minutes at room temperature and worked up as for IXa. In this fashion, 0.81 g. (96%) of a pale, yellow oil, IXb, was obtained [α_D = +33.0 ± 0.5°] (C = 40.0 mg./4 ml. methanol).

Anal. Calcd. for $C_{12}H_{17}NSO_2$: C, 60.23; H, 7.15; N, 5.85; S, 13.38. Found: C, 60.17; H, 7.07; N, 5.91; S, 13.31.

Attempted Racemization of IXa.

A mixture of IXa (0.24 g., 0.0010 mole, α_D = -33.1° ± 0.5°), ammonium chloride (5 g.), water (50 ml.) and tetrahydrofuran (20 ml.) was stirred for 24 hours. The mixture was extracted with ethyl acetate (3 x 25 ml.), these layers dried over magnesium sulfate, and concentrated *in vacuo* affording 0.23 g. (96%) of a yellow oil, α_D = -33.4 ± 0.5°.

REFERENCES AND NOTES

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(3) R. Ratcliffe and R. Rodeharst, *J. Org. Chem.*, **35**, 4000 (1970).

(4) Commercial sample, purchased from Alfa Inorganics.

(5) Both enantiomers of α-phenethyl isocyanate are available from Fairfield Chemical Co.

(6) The authors are indebted to Mr. Robert Frankshun, these laboratories, for technical assistance.