with ether. The extract was washed with water and extracted with 10% hydrochloric acid (200 mL). The aqueous layer was washed with ether, made basic with 40% sodium hydroxide, and extracted with ether. The extract was washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to a brown oil. Short-path, vacuum distillation gave diamine **5** as a yellow oil: 25.4 g (42%); bp 160–170 °C (0.1 mm). Treatment with propionic anhydride as above gave the propionanilide, identical with *cis*-propionanilide **6** as shown by spectroscopic comparison and mixture melting point.

Registry No. **1**, 6947-99-5; *cis*-**2**, 78089-75-5; *trans*-**2**, 78089-84-6; **5**, 78089-76-6; **5**·2HCl, 78089-77-7; **6**, 78089-78-8; **7**, 4840-12-4; **8**, 102-36-3; **10**, 78089-79-9; **11**, 78089-80-2; **12**·2HCl, 78089-81-3; **13**, 78089-82-4; propionic anhydride, 123-62-6; 2-[(dimethylamino)-methyl]cyclopent-1-yl mesylate, 78089-83-5; methanesulfonyl chloride, 124-63-0; 3,4-dichloroaniline, 95-76-1.

Borohydride and Cyanoborohydride Reduction of Thioimonium Salts. A Convenient Route for Transformation of Amides to Amines

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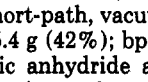
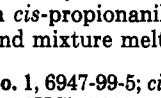
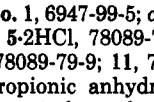
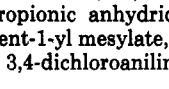
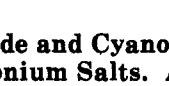
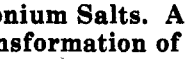
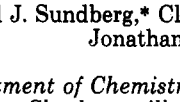
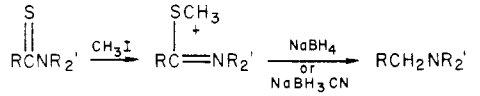
In the synthesis of deethylcatharanthine via the chloroacetamide photocyclization route recently reported from our laboratory,[1] the final stage of the synthesis required reduction of a lactam to an amine in the presence of an ester group, a carbon–carbon double bond, and the electrophile-sensitive indole ring. A sequence involving conversion to the thiolactam, methylation with methyl iodide, and reduction with sodium cyanoborohydride proved to be a very effective method for the overall reduction. Since thioamides have recently been shown to be useful synthetic intermediates,[2] we decided to explore the generality of this reduction sequence. While our work was in progress, Roush reported[3] the use of a similar reaction in one of his synthetic approaches to dendrobine. Raucher and Klein have also independently developed the reaction.[4] The procedure is the sulfur analogue of the Borch method for reduction of amides to amines via imino ethers formed by O-alkylation with trialkyloxonium ions.[5] The principal advantage of the thioamides over amides is their higher nucleophilicity. While the work of Roush and Raucher was carried out using triethyloxonium tetrafluoroborate as the alkylating reagent, we have found that alkylation of the thioamides proceeds to completion at room temperature with methyl iodide in a period of a few hours.

The reduction of tertiary aliphatic amides to amines proceeded smoothly under our conditions. The thioamides were prepared by the standard P_2S_5 method. These were alkylated with methyl iodide in tetrahydrofuran, and the precipitated salts were reduced in methanol with either sodium borohydride or sodium cyanoborohydride. Table I gives the yield of amines.

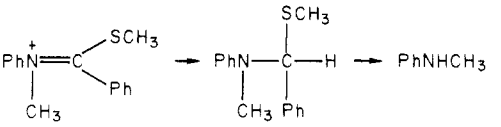
Table I. Reduction of Thioamides

thioamide	yield of amine: $NaBH_4$	yield of amine: $NaBH_3CN$
1a, 	80	70
1b, 	96	89
1c, 	61	77
1d, 	98	69
1e,	60	
1f, 	44[a,b]	
1g, 	44	
1h, 	65[c]	

[a] Reduction in the presence of $ZnCl_2$. [b] Yield determined by NMR. [c] Reduction in the presence of $SnCl_4$.



Under our standard conditions *N*-methylthiobenzanilide gave a considerably lower yield than was observed for the aliphatic amides, and some effort was devoted to examining the reaction conditions to see if the yield could be improved. Under the standard conditions *N*-methylaniline was found to be the major product, suggesting hydrolysis of the partially reduced intermediate. Inclusion of zinc

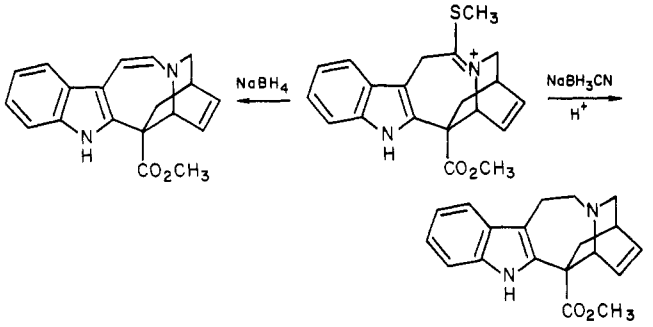


chloride to promote elimination of methanethiol improved the yield somewhat, but the yield remained below that obtained for the aliphatic amides. Similarly, the reduction of thioacetanilide proceeded in low yield under the standard conditions, but inclusion of stannic chloride in the reduction mixture resulted in a 65% yield of *N*-ethylaniline.

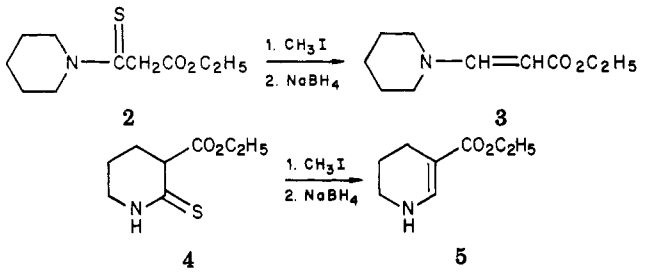
In the case of deethylcatharanthine we had noted enamine formation rather than complete reduction when $NaBH_4$ (basic solution) was used, while $NaBH_3CN$ (under acidic conditions) gave complete reduction to the amine. No enamine formation was noted for the compounds **1b** or **1d**. The result with deethylcatharanthine, therefore, is evidently a reflection of the special bridgehead nature of the thiolactam.[6] Placement of a carboethoxy group on the 2-position of the thioacyl moiety resulted in partial reduction to the conjugated enamine intermediate in

(1) R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, **45**, 3382 (1980).
(2) Y. Tamaru, T. Harada, and Z. Yoshida, *J. Am. Chem. Soc.*, **101**, 1316 (1979); Y. Tamaru, T. Harada, and Z. Yoshida, *ibid.*, **102**, 2392 (1980); Y. Tamaru, M. Kagotani, and Z. Yoshida, *J. Org. Chem.*, **45**, 5221 (1980); Y. Tamaru, M. Kagotani, and Z. Yoshida, *ibid.*, **44**, 2816 (1979); Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, *J. Am. Chem. Soc.*, **100**, 5221 (1978); Y. Tamaru, T. Harada, and Z. Yoshida, *ibid.*, **100**, 1923 (1978).
(3) W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980).
(4) S. Raucher and P. Klein, *Tetrahedron Lett.*, 4061 (1980).
(5) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(6) Even lithium aluminum hydride reduction gives only partial reduction of lactams in this skeletal system: W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967); W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *ibid.*, **90**, 1650 (1968).

0022-3263/81/1946-3730$01.25/0

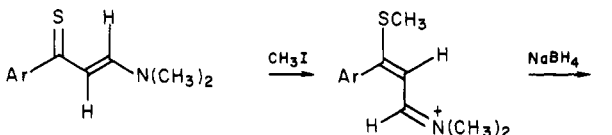


modest yield (25%), when carried out under basic conditions as illustrated with compounds **2** and **4**. Reduction

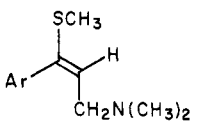


of **2** with sodium cyanoborohydride at pH 4 led to complete reduction in 55% yield. The reduction of β-carboethoxy enamines under similar conditions has been demonstrated by Borch and co-workers.[7]

Finally, we examined several vinylogous thioamides. The requisite β-aroylenamines were prepared from acetophenones as described by Gupton et al.[8] and converted to the thiones by reaction with P_2S_5 in benzene.[9] Methylation was rapid with methyl iodide. The resulting salts were reduced in 50–80% yields to the vinyl sulfides **8a–8c**.

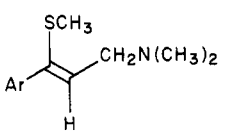


6a, Ar = phenyl
b, Ar = *p*-nitrophenyl
c, Ar = *p*-methoxyphenyl



8a–c

This reflects selective 1,2 reduction of the conjugated β-(methylthio)imonium ion **7**. The NMR spectra of the product vinyl sulfides indicate less than 5% of the *Z* stereoisomer **9a–9c** is formed in the reduction. In each sample of **8**, a weak triplet can be seen ~0.4 ppm downfield of the triplet assigned to the vinyl proton of **8** and is assumed to be due to the stereoisomeric vinyl sulfides, **9a–9c**.



9a–c

The compounds were not isolated, however. The stereochemistry is assigned on the basis of chemical shift additivity rules[10] (calculated for **8a**, 5.60; found, 5.58) and is in consonance with the assignments of the closely analogous *E* and *Z* isomers of 1-(methylthio)-1-propenylbenzene: *Z* isomer, 5.89; *E* isomer, 5.70.[11]

Our results, along with those of Raucher,[4] indicate wide applicability of the reduction thioimonium salts for preparation of amines under mild conditions. Our results further show that certain conjugated systems will lead to partial reduction.

Experimental Section

General Procedure for Preparation of Thioamides 1a–1g. A solution of the amide (2.5 mmol) in dioxane (15 mL), which has been distilled from sodium benzophenone ketyl, was treated with P_2S_5 (3.0 mmol), and the heterogeneous mixture was stirred at room temperature for 2 h. The progress of the reaction was followed by TLC and, if necessary, the solution was warmed to 35 °C until the amide was consumed. The dioxane was decanted from the residual solid and filtered. Evaporation of the dioxane left crude thioamide, which was purified by distillation or recrystallization. Yields were 50–70% **1a**, 70% yield, mp 46–48 °C; **1b**, 64%, mp 73–74 °C; **1c**, 65%, mp 62–65 °C; **1d**, 51%, mp 71–72 °C; **1e**, oil; **1f**, 48%, mp 96–97 °C; **1g**, oil.

General Procedures for Methylation and Reduction of Thioamides 1a–1h. The thioamide (1–5 mmol) was dissolved in anhydrous THF (10–25 mL) and treated with a fivefold excess of methyl iodide. The reaction mixture was stirred at room temperature until disappearance of the thioamide was complete as judged by TLC (0.5–12 h). In most cases the salt precipitated. The THF was evaporated under reduced pressure and the residual salt dried in vacuo. The dry salt was then dissolved in dry methanol (25–50 mL) and treated cautiously with 1.1 molar equiv of solid sodium borohydride (vigorous gas evolution) or sodium cyanoborohydride. When sodium cyanoborohydride was to be used as the reducing agent, acetic acid (20 mL, 1:1 acetic acid/water) was added to the methanolic solution of the thioamide. Upon addition of the sodium borohydride there was immediate gas evolution, including methanethiol (stench). The reaction mixture was stirred for 2 h and then made strongly alkaline with 20% NaOH solution. The mixture was extracted with ether, and the extracts were dried and evaporated. For thioamides **1a–1d** and **1g**, the residual amine was >95% pure as judged by NMR, and the yield was determined by quantitative gas chromatography at 90 °C on a SE-30 column using bibenzyl (**1a**, **1b**) or biphenyl (**1c**, **1d**) as the internal standard. The yields of **1g** and **1h** were determined by weight after confirmation of purity by NMR. The yield of **1e** is corrected for contamination by *N*-methylaniline, as determined by NMR.

Procedure for Isolation of Distilled Amine. (Phenylthioacetyl)piperidine (**1d**) (2.0 g) was dissolved in dry THF (50 mL) and treated with a fivefold excess of methyl iodide. The solution was stirred overnight and then filtered to give 2.9 g (90%) of the methiodide salt. This was dissolved in dry methanol (50 mL) and treated cautiously with $NaBH_4$ (0.30 g) and stirred 1 h at room temperature. The solution was then made strongly basic with 20% NaOH solution and extracted with ether. The extract was dried over K_2CO_3, evaporated on a rotary evaporator, and distilled to give 0.8 g (53%) of pure *N*-(2-phenylethyl)piperidine.

Reduction of Thioacetanilide (1h) in the Presence of Stannic Chloride. Thioacetanilide was converted to the methiodide salt in the usual way. The salt (0.5 g) was suspended in 5 mL of dry dimethoxyethane and treated with $NaBH_4$ (450 mg) and tin(IV) chloride dietherate (1.0 g). The solution was stirred for 2 h at 0 °C and then carefully hydrolyzed. The solution was made basic with 5% K_2CO_3 solution and extracted to give *N*-ethylaniline (65%), which was pure by NMR.

(7) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(8) J. T. Gupton, C. Colon, C. R. Harrison, M. J. Lizzi, and D. E. Polk, *J. Org. Chem.*, **45**, 4522 (1980).
(9) Essentially the method for F. Clesse and H. Quiniou; *Bull. Soc. Chim. Fr.*, 1940 (1969). For an alternative method, see Y. Lin and S. A. Lang, Jr., *J. Org. Chem.*, **45**, 4857 (1980).
(10) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966); U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).
(11) M. Mikołajczyk, S. Grzejszczak, A. Chefczyńska, and A. Zatorski, *J. Org. Chem.*, **44**, 2967 (1979).
(12) J. Liebscher and H. Hartmann, *Z. Chem.*, **12**, 417 (1972).

Preparation of Ethyl 3-Piperidino-3-thioxopropionate (2). Ethyl malonylpiperidine (4.75 g, 23 mmol) was dissolved in toluene (100 mL) and treated with 5.1 g (23 mmol) of P_2S_5. The reaction mixture was stirred at room temperature until the amide had reacted completely (1 h). The solution was filtered, and the filtrate was dried and evaporated to give **2** (4 g, 76%) as an oil: NMR 1.28 (3 H, t), 1.70 (6 H, m), 3.60 (2 H m), 4.02 (2 H, s), 4.20 (2 H, q, overlapping a multiplet at 4.24 (2 H)).

Preparation of 3-(Carboethoxy)-2-thioxopiperidine (4). A solution of 3-(carboethoxy)-2-piperidone (3.0 g, 17.5 mmol) in toluene (100 mL) was treated with (3.9 g, 17.5 mmol) of P_2S_5. The mixture was stirred at room temperature until the starting material had been completely consumed. The toluene was then decanted. The insoluble precipitate was treated with cold 10% NaOH and extracted with ether. The ether and toluene solutions were combined and washed with aqueous NaOH, dried, and evaporated to give an oil. Crystallization from ethanol gave 1.2 g of **4** (36%): mp 113–114 °C; NMR 1.32 (3 H, t), 2.00 (2 H, m), 3.40 (2 H, m), 3.80 (1 H, t), 4.15 (2 H, q), 9.3 (1 H, br s).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.09; H, 7.06; N, 7.45.

Reduction of Compound 2. A. $NaBH_4$ at Basic pH. A solution of **2** (2.0 mmol) in THF was treated with methyl iodide (10.0 mmol) and stirred overnight. Partial precipitation of the salt occurred. The THF was evaporated, and the residue was washed with ether, dissolved in methanol, treated with sodium borohydride, and stirred for 2 h. The basic solution was poured into water, extracted with ether, dried, and evaporated to give an oil (26% yield) identified by NMR as **3** containing <10% of the fully reduced amine.

B. $NaBH_3CN$ at Acidic pH. A solution of 2.0 mmol of **2** in 10 mL of THF was treated with 10.0 mmol of methyl iodide. The solution was stirred overnight and the THF evaporated, leaving a yellow salt. The salt was dried in vacuo, dissolved in absolute ethanol (15 mL) and a trace of bromcresol green indicator was added. Sodium cyanoborohydride (22.0 mmol) was added, resulting in change of the indicator to dark blue. Ethanolic HCl was added dropwise over 1 h to maintain acidity as indicated by the yellow color of the indicator. At this point the solution was acidified to pH 1 and stirred overnight to hydrolyze any amine–borane adduct. The solution was diluted with water and extracted with ether, and the aqueous layer was cooled and carefully brought to pH 9 with cold 10% NaOH solution. Extraction with ether, drying, and evaporation gave a 53% yield of ethyl 3-piperidinopropionate as identified by the NMR spectrum: 1.23 (3 H, t), 1.50 (6 H, m), 2.40 (4 H, m), 2.60 (4 H, m), 4.20 (2 H, q).

Reduction of Compound 4 with $NaBH_4$. A solution of **4** (2.3 mmol) in THF was treated with methyl iodide. The salt precipitated and the THF was removed by evaporation. The dried salt was dissolved in methanol (15 mL) and treated cautiously with $NaBH_4$. After being stirred 2 h, the reaction mixture was separated into neutral and basic fractions by extraction. The neutral fraction contained only **5** (25%), identified by NMR comparison with an authentic sample. No significant basic product was obtained.

General Procedure for Vinylogous Thioamides 6a–6c. The 1-aryl-3-(dimethylamino)prop-2-enones used as starting materials were prepared from the appropriate acetophenone as described by Gupton.[8] The enaminone (15 mmol) in 100 mL of dry benzene was treated with P_2S_5 (15 mmol), and the solution was refluxed until disappearance of the starting material was complete. The dark benzene solution was decanted from the solid and the solid was washed with additional benzene. The benzene was washed with sodium bicarbonate, dried, and concentrated. The concentrated solution was passed through a silica gel column using 20% ether in benzene for elution. The intensely orange-brown band containing product was collected and concentrated, and the residue was crystallized from benzene–hexane. **6a**, 24%, mp 116–118 °C (lit.[12] mp 112–115 °C; **6b**, 32%, mp 130–140 °C dec; **6c**, 18%, mp 107 °C (lit.[12] mp 105–106 °C.

Anal. **6b**: Calcd for $C_{11}H_{12}N_3O_2S$: C, 55.9; H, 5.1. Found: C, 56.0; H, 5.1.

General Procedure for Methylation and Reduction of 6a–6c. A solution of **6** (0.15 mmol) in anhydrous THF (5 mL) was treated with 0.3 mL of methyl iodide and stirred at room temperature for 2 h. A yellow salt precipitated. The salt was separated by filtering or decantation and rinsed with ether. The salt was then dissolved in anhydrous methanol (5 mL) and treated very cautiously over 5 min with solid $NaBH_4$ (50 mg). Vigorous gas evolution occurs with each addition of sodium borohydride. After 0.5 h the reaction solution was poured into 2% HCl solution and extracted with ether. Basification and extraction with ether gave the amine, which was purified by distillation or crystallization. **8a**: 67% yield, bp ~ 100 °C (0.1 mm); NMR 2.15, 3.17 (overlapping s, 9 H), 2.84 (2 H, d), 5.58 (1 H, t), 7.31 (5 H, s). **8b**: 53% yield, mp 52–53 °C from hexane; NMR 2.15 (6 H, s), 2.20 (3 H, s), 2.80 (2 H, d), 5.70 (1 H, t), 7.45 (2 H, d), 8.24 (2 H, d). **8c**: 78% yield, bp ~ 125 °C (0.1 mm); NMR 2.14 (9 H, s), 2.90 (2 H, d), 3.74 (3 H, s), 5.56 (1 H, t), 6.88 (2 H, d), 7.20 (2 H, d).

Anal. **8a**: Calcd for $C_{12}H_{17}NS$: C, 69.5; H, 8.3. Found: C, 69.3; H, 8.3. **8b**: Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.1; H, 6.4. Found: C, 57.1; H, 6.4. **8c**: Calcd for $C_{13}H_{19}NSO$: C, 65.8; H, 8.1. Found: C, 65.7; H, 8.1.

Registry No. **1a**, 15563-45-8; **1a** methyl iodide, 78089-85-7; **1b**, 18732-58-6; **1b** methyl iodide, 73160-83-5; **1c**, 15563-40-3; **1c** methyl iodide, 61135-82-8; **1d**, 24815-46-1; **1d** methyl iodide, 78089-86-8; **1e**, 15563-35-6; **1e** methyl iodide, 78089-87-9; **1f**, 2628-58-2; **1f** methyl iodide, 57513-33-4; **1g**, 78089-88-0; **1g** methyl iodide, 78089-89-1; **1h**, 637-53-6; **1h** methyl iodide, 78089-90-4; **2**, 57005-87-5; **3**, 19524-67-5; **4**, 78089-91-5; **5**, 3335-05-5; (*E*)-**6a**, 65672-85-7; (*E*)-**6b**, 78089-92-6; (*E*)-**6c**, 22292-83-7; (*E*)-**7a**, 78089-93-7; (*E*)-**7b**, 78089-94-8; (*E*)-**7c**, 78089-95-9; (*E*)-**8a**, 78089-96-0; (*E*)-**8b**, 78089-97-1; (*E*)-**8c**, 78089-98-2; *N*-benzoylpyrrolidine, 3389-54-6; *N*-(phenylacetyl)pyrrolidine, 3389-53-5; *N*-benzoylpiperidine, 776-75-0; *N*-(phenylacetyl)-piperidine, 3626-62-8; *N*,*N*-dibutylbenzamide, 25033-65-2; *N*-methyl-*N*-phenylbenzamide, 1934-92-5; *N*-*sec*-butylbenzamide, 879-71-0; ethyl malonylpiperidine, 34492-46-1; 3-(carboethoxy)-2-piperidone, 3731-16-6; ethyl 3-piperidinopropionate, 19653-33-9; (*E*)-phenyl-3-(dimethylamino)prop-2-enone, 1131-80-2; (*E*)-1-(*p*-nitrophenyl)-3-(dimethylamino)prop-2-enone, 78089-99-3; (*E*)-1-(*p*-methoxyphenyl)-3-(dimethylamino)prop-2-enone, 78090-00-3; *N*-benzylpyrrolidine, 29897-82-3; *N*-(2-phenylethyl)pyrrolidine, 6908-75-4; *N*-benzylpiperidine, 2905-56-8; *N*-(2-phenylethyl)piperidine, 332-14-9; *N*,*N*-dibutylbenzylamine, 4383-27-1; *N*-methylaniline, 100-61-8; *N*-*sec*-butylbenzylamine, 46120-25-6; *N*-ethylaniline, 103-69-5; $NaBH_4$, 16940-66-2; $NaBH_3CN$, 25895-60-7.

Isotopic Labeling Studies of the Thermal Rearrangement of Phenyloxirane to Phenylethanal[1]

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The thermal rearrangement of phenyloxirane (**1**) to phenylethanal (**2**) was reported by Watson and Young[2] to take place with first-order kinetics and without the production of acetophenone, which had been observed as an additional minor rearrangement product of photolysis of phenyloxirane[3] or of its reaction in the presence of sodium iodide, 1-iodopropane, and dimethyl sulfoxide.[4] The thermal rearrangement could be carried out neat or in solvents such as benzene, toluene, or xylene, either in sealed Pyrex-glass ampules or in a stainless-steel reaction vessel.[5,6] The yields in stainless-steel vessels decreased

(1) Generous support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
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