Reduction of **4b** with lithium tetrahydroaluminate in a similar procedure affords a colorless liquid identified as **6b**; yield: 92%.

6b: M.S.: $m/e = 224$ (M$^+$), 209 (M$^+$ —CH$_3$), 121, 105, 89, 77, 59.

I.R. (neat): $\nu_{max} = 2900$; 1600; 1490; 1460; 1380; 1103; 760; 698 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): $\delta = 1.34$ (d, 3H); 3.28 (s, 3.0H); 3.30–3.60 (m, 8.1H); 4.36 (q, 0.9H); 7.28 ppm (s, 5.0H).

Preparation of Alkyl-Substituted 15-Crown-5 Ethers 5 (n = 4):

Compound **3g** (35.7 g, 0.1 mol) is dissolved in dioxan (120 ml) and the solution is added to a suspension of powdered sodium hydroxide (5.0 g) in dioxan (100 ml) at room temperature. The mixture is stirred for 10 h at 80° and for further 8 h at 100°. After sodium bromide has been filtered off, the dioxan is removed from the filtrate to leave a yellow liquid; yield: 24.4 g. The product is distilled in vacuo and the fractions of b.p. 120–125°/0.2 torr are collected; yield: 8.8 g (32%). Further purification on a column (Silica gel, hexane/acetone, 5:1) affords pure 2-butyl-15-crown-5 (**5g**, R^1 = C$_4$H$_9$, R^2 = H, n = 4) as a colorless liquid; $n_D^{20} = 1.4635$.

C$_{14}$H$_{28}$O$_5$ calc.   C 60.84   H 10.21
(276.3)   found   60.56   10.10

M.S.: $m/e = 276$ (M$^+$), 219, 133, 89, 87, 73, 59, 45; relative intensities: 0.5, 3, 21, 63, 45, 40, 68, 100%, respectively.

I.R. (neat): $\nu_{max} = 2910$; 2830; 1470; 1350; 1295; 1130; 985; 940; 850 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): $\delta = 0.90$ (t, 3H); 1.34 (m, 6H); 3.24–3.72 ppm (multiplets, 19H).

By a similar procedure, 2-hexyl-15-crown-5 (**5j**, R^1 = C$_6$H$_{13}$, R^2 = H, n = 4) is obtained from **3j** as a colorless liquid; crude yield: 29%; b.p. 130–134°/0.1 torr; $n_D^{20} = 1.4620$.

C$_{16}$H$_{32}$O$_5$ calc.   C 63.12   H 10.60
(304.4)   found   62.72   10.68

M.S.: $m/e = 304$ (M$^+$), 219, 133, 89, 87, 73, 59, 45; relative intensities: 0.5, 5, 18, 60, 38, 32, 60, 100%, respectively.

I.R. (neat): $\nu_{max} = 2910$, 2830, 1470, 1350, 1295, 1130, 980, 940, 850 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): $\delta = 0.90$ (t, 3.1H), 1.32 (m, 9.8H), 3.16–3.72 ppm (multiplets, 19H).

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[1] C. J. Pedersen, H. K. Frensdorff, *Angew. Chem.* **84**, 16 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 16 (1972).

[2] J. J. Christensen, D. J. Eatough, R. M. Izatt, *Chem. Rev.* **74**, 351 (1974).

[3] G. W. Gokel, H. D. Durst, *Synthesis* **1976**, 168; *Aldrichimica Acta* **9**, 3 (1976).

[4] M. Cinquini, P. Tundo, *Synthesis* **1976**, 516.

[5] D. Clement, F. Damm, J-M Lehn, *Heterocycles* **5**, 477 (1976).

[6] A. Roedig in: Houben-Weyl *Methoden der Organischen Chemie* 4th Edit., E. Müller, Ed., Georg Thieme Verlag Stuttgart, Vol. 5/4, 1960, p. 142.

[7] J. Chretien, M. Durand, G. Mouvier, *Bull. Soc. Chim. Fr.* **1969**, 1966.

[8] A. Jovtscheff et al., *Monatsh. Chem.* **97**, 1620 (1966).

[9] M. Lafosse, M. Savignac, *Chromatographia* **6**, 415 (1973).

[10] A. Jovtscheff et al., *Z. Chem.* **15**, 191 (1975).

[11] R. A. Bartsch, D. K. Roberts, *Tetrahedron Lett.* **1977**, 321.

[12] F. L. Cook et al., *Tetrahedron Lett.* **1974**, 4029.

[13] G. Jones, C. R. Ranson, C. B. Reese, *Synthesis* **1976**, 515.

[14] V. M. Micovic, M. L. J. Mihailovic, *J. Org. Chem.* **18**, 1190 (1953).

Reactions of Sodium Borohydride in Acidic Media; V. Reduction and Alkylation of Oximes with Carboxylic Acids; A New Synthesis of N,N-Dialkylhydroxylamines[1]

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We wish to report that the action of sodium borohydride on oximes **1** in carboxylic acids leads to N,N-dialkylhydroxylamines **2**.
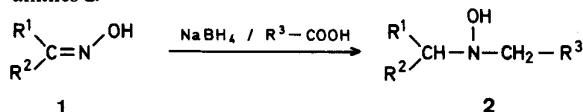
Our earlier work on the reduction of indoles, quinolines, and isoquinolines[2] and the alkylation of amines[2,3] and Borch's observation that oximes can be reduced to N-alkylhydroxylamines with sodium cyanoborohydride in acidic methanol[4] suggested to us that sodium borohydride in carboxylic acids would accomplish the reduction/alkylation of oximes **1**, leading to a new and potentially versatile synthesis of N,N-dialkylhydroxylamines **2**. We have examined several oximes and carboxylic acids under three different reaction conditions (Methods A–C) and find that the reaction is quite general, although the yields of **2** range from 36–87%. No particular advantage accrues from using one reaction method over another, as each of the three methods is capable of giving good yields of **2**. Of the oximes studied only benzophenone oxime and dibenzyl ketoxime fail to react under these conditions. Most of our work has involved ketoximes but aldoximes appear to react equally well, except for the difficulty noted later.

The reaction presumably involves initial reduction of **1** to the N-alkylhydroxylamine followed by alkylation. Indeed, we find that cyclohexanone oxime (**3**) is smoothly reduced to N-cyclohexylhydroxylamine (**4**) with sodium borohydride/acetic acid under mild conditions or in higher yield with sodium cyanoborohydride/acetic acid. We have previously shown that these latter conditions do not give significant N-alkylation[2]. By comparison, Borch reports a 66% yield of **4** from the reaction of **3**[4].
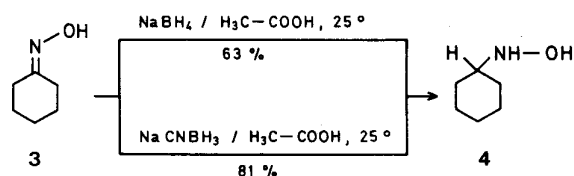
The variable yields may in part be due to the relative instability[5] and/or water solubility of some of the N,N-dialkylhydroxylamines **2**. In some cases we have observed by mass spectrometry or have isolated products corresponding to overreduction[6] and subsequent alkylation, and products resulting from condensation of the initially formed monoalkylhydroxylamine with oxime, followed by reduction to the symmetrical dialkylhydroxylamine. This latter pathway was observed by Borch during his reduction of aldoximes[4]. For example, in the reaction of butanal oxime with sodium borohydride/acetic acid we see in addition to **2o** an ion in the mass spectrum of the crude product corresponding to N,N-di-n-butylhydroxylamine. In one case using Method C this

product was isolated. Similarly, benzaldoxime gives some N,N-dibenzylhydroxylamine in addition to $2r$. 2,2-Dimethyl-propanoic acid/sodium borohydride gives very poor yields of dialkylhydroxylamines from oximes (not in Table) and in the reaction with benzaldoxime we observe by mass spectrometry N,N-dineopentylbenzylamine and N-neopentyldibenzylamine, products of overreduction and subsequent alkylation. These side products are often difficult to remove and may be responsible for the impure oxalates that are obtained in some cases, especially with the aldoximes. Further work is necessary to ameliorate the generality of the reaction of oximes with sodium borohydride/carboxylic acids.

In spite of these drawbacks and the limitations inherent in the method, it is excellent for preparing unsymmetrical N,N-dialkylhydroxylamines of type 2 from ketoximes, which of course are readily available from ketones, and offers an attractive alternative to the existing general methods[7]: alkylation of N-alkylhydroxylamines, oxidation of secondary amines, pyrolysis of tertiary amine oxides, and reduction of nitrones.

Preparation of N-Isopropyl-N-propylhydroxylamine (2b); Method A/Workup A:

To a stirred solution of acetone oxime (0.73 g, 10 mmol) in propanoic acid (20 g) at 50° under nitrogen are added sodium borohydride pellets (Ventron) (2.3 g, 61 mmol) over 5 h. The mixture is heated at 50° for 5 h, allowed to cool, and made basic with 50% aqueous sodium hydroxide. The mixture is extracted with ether. The ether extract is extracted with 1 normal hydrochloric acid. The acid extract is made basic with aqueous sodium hydroxide and extracted with ether. The ether extract is dried with anhydrous potassium carbonate and concentrated in vacuo. The resulting yellow oil (0.81 g) is distilled in vacuo to give N-isopropyl-N-propylhydroxylamine (2b) as a colorless oil; yield: 0.79 g (68%); b.p. 55–56°/10 torr.

I.R. (liquid film): $\nu_{max} = 3280$; 2995; 1465; 1380; 1360 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 1.00$ (t, 3H); 1.06 (d, 6H); 1.55 (m, 2H); 2.64 (t, 2H); 2.97 (m, 1H); 7.70 ppm (s, 1H).

The oxalate derivative of 2b is prepared by adding a solution of 2b (0.156 g, 1.3 mmol) in ether (5 ml) dropwise to a solution of dry oxalic acid (0.16 g, 1.8 mmol) in ether (10 ml). The resulting precipitate (0.14 g, 52% yield) is recrystallized seven times from absolute ethanol; m.p. 124–124.5°.

$C_8H_{17}NO_5$ calc. C 46.37 H 8.27 N 6.76
(207.2) found 46.39 8.36 6.65

Preparation of N-Cyclohexyl-N-ethylhydroxylamine (2i); Method B/Workup B:

To stirred acetic acid (40 ml) at 30° under nitrogen are added sodium borohydride pellets (1.0 g, 26 mmol). Upon dissolution, cyclohexanone oxime (3.39 g, 30.0 mmol) and additional sodium borohydride pellets (1.0 g) are added simultaneously. The mixture is heated to 40° and additional sodium borohydride pellets (1.0 g) are added (total: 3.0 g, 79 mmol). Heating at 40° is continued for 5 h. The mixture is allowed to cool, made basic with 50% aqueous sodium hydroxide, and extracted with ether. The ether extract is dried, concentrated in vacuo, and distilled to give N-cyclohexyl-N-ethylhydroxylamine (2i) as a colorless oil; yield: 2.19 g (51%); b.p. 65–67°/0.35 torr.

I.R. (liquid film): $\nu_{max} = 3280$; 2965; 2900; 1455; 1080 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 1.15$ (t, 3H); 1.6 (m, 10H); 2.6 (m, 1H); 2.75 (q, 2H); 7.47 ppm (s, 1H).

The oxalate is prepared in 68% yield as above and has m.p. 155–156° after five recrystallizations from ethanol.

$C_{18}H_{36}N_2O_6$ calc. C 57.42 H 9.64 N 7.44
(376.5) found 57.14 9.86 7.16

Preparation of N-Benzyl-N-n-butylhydroxylamine (2r); Method C/Workup C:

To a stirred paste of benzaldoxime (1.21 g, 10.0 mmol) and sodium borohydride powder (2.0 g, 53 mmol) at 0° under nitrogen is added butanoic acid (25 ml) dropwise over 2 h. The mixture is then heated at 40° for 4 h, an additional amount of sodium borohydride (0.37 g, 10 mmol) is added and the mixture is heated for 1 h more. Workup as in Workup B gives a yellow oil which is dissolved in ether (2 ml) and added to a solution of oxalic acid (1.50 g, 16.7 mmol) in ether (5 ml) to give the crude oxalate; yield: 1.86 g (69%);. The oxalate is dissolved in water, made basic with aqueous sodium hydroxide, and extracted with ether. After the usual workup, the resulting oil is distilled to give N-benzyl-N-n-butylhydroxylamine (2r) as a colorless oil; yield: 1.04 g (58%); b.p. 84–85°/0.15 torr.

I.R. (liquid film); $\nu_{max} = 3280$; 3060; 2985; 2900; 1495; 1450 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 0.95$ (m, 3H, virtual coupling); 1.4 (m, 4H); 2.60 (t, 2H); 3.63 (s, 2H); 7.22 (s, 5H); 7.80 ppm (s, 1H).

M.S.: $m/e = 179.1316$ (calc. 179.1310).

Preparation of N-Cyclohexylhydroxylamine (4) using Sodium Cyanoborohydride/Acetic Acid:

To stirred acetic acid (25 ml) at 25° under nitrogen are added cyclohexanone oxime (3; 1.16 g, 10.3 mmol) and sodium cyanoboro-

Table. Reaction of Oximes 1 with Sodium Borohydride in Carboxylic Acids

Product No.	R^1	R^2	R^3	Method^a/ Workup^b	Reaction conditions Temp./Time	Yield^c of 2 [%]	b.p./torr or m.p.	m.p. of Oxalate^d	Molecular Formula^e
2a	CH$_3$	CH$_3$	CH$_3$	A/A	50°/24 h	36	45–48°/10	101–102°	C$_7$H$_{15}$NO$_5$ (193.2)
2a	CH$_3$	CH$_3$	CH$_3$	B/A	40°/4 h	38			
2b	CH$_3$	CH$_3$	C$_2$H$_5$	A/A	50°/20 h	68	55–56°/10	124–124.5°	C$_8$H$_{17}$NO$_5$ (207.2)
2c	CH$_3$	CH$_3$	i-C$_3$H$_7$	A/A	50°/20 h	52	55–61°/10	142–143°	C$_9$H$_{19}$NO$_5$ (221.3)
2d	CH$_3$	C$_2$H$_5$	CH$_3$	A/B	45°/20 h	63	65–67°/17	92–93°	C$_8$H$_{17}$NO$_5$ (207.2)
2e	CH$_3$	C$_2$H$_5$	C$_2$H$_5$	C/C	40°/5 h	61	66–69°/10	97–98°	C$_7$H$_{17}$NO^f (131.2)
2f	CH$_3$	t-C$_4$H$_9$	CH$_3$	A/B	50°/6 h	75	70–71°/17	115.5–116°	C$_{10}$H$_{21}$NO$_5$ (235.3)
2g	CH$_3$	t-C$_4$H$_9$	C$_2$H$_5$	A/A	50°/30 h	53	68–71°/10	147–147.5°	C$_{11}$H$_{23}$NO$_5$ (249.3)
2h	CH$_3$	t-C$_4$H$_9$	i-C$_3$H$_7$	A/A	50°/30 h	47	68–73°/10		C$_{10}$H$_{23}$NO^g (173.3)

Table. (Continued)

Product No.	R¹	R²	R³	Method[a]/ Workup[b]	Reaction conditions Temp./Time	Yield[c] of 2 [%]	b.p./torr or m.p.	m.p. of Oxalate[d]	Molecular Formula[e]
2i		—(CH₂)₅—	CH₃	B/B	40°/5 h	51	65–67°/0.35	155–156°	C₁₈H₃₆N₂O₆ (376.5)
2i		—(CH₂)₅—	CH₃	A/A	55°/72 h	58			
2j		—(CH₂)₅—	C₂H₅	A/A	55°/20 h	87	68–70°/0.25	136–137°	C₁₁H₂₁NO₅ (247.3)
2k	CH₃	C₆H₅	CH₃	A/C	55°/31 h	41	68–69°/0.2	136–137°	C₂₂H₃₂N₂O₆ (420.5)
2l	CH₃	CH₂C₆H₅	CH₃	A/B	55°/20 h	68[h]	97–105°/0.35	172–173° (Lit.[8] 161–162°)	C₂₄H₃₆N₂O₆ (448.6)
2m	CH₃	CH₂C₆H₅	C₂H₅	C/C	40°/4 h	47[h]	107–110°/0.3	142–143° (Lit.[9] 142–143°)	C₁₄H₂₁NO₅ (283.3)
2n	CH₃	CH₂C₆H₅	n-C₃H₇	C/B	40°/4 h	70[h]	109–116°/0.2	165–166° (Lit.[8] 157–159°)	C₁₅H₂₃NO₅ (297.4)
2o	H	n-C₃H₇	CH₃	A/B	5°, 45°/4 h	55	64–68°/11	98–99°	C₆H₁₅NO[i] (117.1)
2p	H	C₆H₅	CH₃	B/B	40°/5 h	56	75–77°/0.35 (Lit.[10] 88°/1.1)	111–112°	C₉H₁₃NO[j] (151.2)
2q	H	C₆H₅	C₂H₅	A/B	25°/72 h	72	77–78°/0.2	120–120.5°	C₁₂H₁₇NO₅ (255.3)
2r	H	C₆H₅	n-C₃H₇	C/C	40°/5 h	58	84–85°/0.15	119–121°	C₁₁H₁₇NO[k] (179.3)
2s	H	C₆H₅	i-C₃H₇	C/B	40°/4 h	65	60–61°	140.5°	C₁₃H₁₉NO₅ (269.3)

[a] Method A: Sodium borohydride pellets are added to a solution of oxime in the neat carboxylic acid at the specified temperature and the mixture is heated.

Method B: The oxime is added to a mixture of sodium borohydride pellets in the neat carboxylic acid and the mixture is heated.

Method C: A mixture of the oxime and powdered sodium borohydride at 0° is treated with the carboxylic acid and the mixture is heated.

[b] Workup A: The reaction mixture is made basic and extracted with ether. The ether extracts are extracted with dilute hydrochloric acid. The acid extracts are basified and extracted with ether. Drying, concentration, and distillation afford the product.

Workup B: The reaction mixture is made basic and extracted with ether. Drying, concentration, and distillation afford the product.

Workup C: As in workup B except that the crude product is treated with oxalic acid in ether. The crude oxalate is dissolved in water, made basic, and extracted with ether. The product is isolated as in the above workup methods.

[c] Yields represent distilled or, in one case (2s), recrystallized product. Products exhibited satisfactory I.R. and ¹H-N.M.R. spectra. The reactions have not been optimized.

[d] Oxalates were recrystallized several times from ethanol, ethanol/ether, or dichloromethane.

[e] Unless otherwise noted all oxalates gave satisfactory microanalyses (C ± 0.28 %, H ± 0.25 %, N ± 0.28 %).

[f] The oxalate, recrystallized six times, did not analyze correctly. M.S.: m/e = 130.1241 (M⁺ − 1, calc. 130.1232).

[g] A crystalline oxalate was not obtained. M.S.: m/e = 172.1689 (M⁺ − 1, calc. 172.1701).

[h] Some oxime is present in the product.

[i] The oxalate, recrystallized five times, analyzed slightly outside acceptable limits. M.S.: m/e = 116.1077 (M⁺ − 1, calc. 116.1075).

[j] The oxalate analyzed as a 1:1 mixture of C₁₁H₁₅NO₅ and C₂₀H₂₈N₂O₆. M.S.: m/e = 151.0977 (M⁺, calc. 151.0997).

[k] The oxalate, recrystallized four times, did not analyze correctly. M.S.: m/e = 179.1316 (M⁺, calc. 179.1310).

hydride (0.93 g, 15 mmol). The mixture is stirred for 3 h and then water is added. The mixture is made basic with sodium hydroxide (pellets) and the resulting white solid is collected. The aqueous filtrate is extracted with ether and the ether extract is dried and concentrated in vacuo to afford a white solid. The combined solids are recrystallized from ether to give N-cyclohexyl-hydroxylamine (4) as colorless flakes; yield: 0.96 g (81 %); m.p. 138–139°; Lit.[4] m.p. 138–139°.

A longer reaction time (20 h) using Method C conditions gave N-cyclohexyl-N-ethylhydroxylamine (2i) in 44 % yield.

Preparation of N,N-Di-n-Butylhydroxylamine:
To stirred acetic acid (15 ml) at 15° is added 1 pellet of sodium borohydride. Upon dissolution, butanal oxime (0.88 g, 10 mmol) is added. The mixture is heated to 40–50° over the period of 1 h and a second pellet of sodium borohydride is added (total: 0.47 g, 12 mmol). After 2 h total reaction time the mixture is cooled, diluted with water (50 ml), and made basic with sodium

hydroxide (pellets). The resulting white solid is collected, washed, and dried to afford N,N-di-n-butylhydroxylamine as off-white flakes; yield 0.31 g (21 %); m.p. 48.5–50.5°; Lit.[11] 52–53°.

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[1] Part IV: G. W. Gribble, R. M. Leese, B. E. Evans, Synthesis **1977**, 172.

[2] G. W. Gribble et al., *J. Am. Chem. Soc.* **96**, 7812 (1974).
G. W. Gribble, P. W. Heald, *Synthesis* **1975**, 650.

[3] P. Marchini et al., *J. Org. Chem.* **40**, 3453 (1975).

[4] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).

[5] For example, see: A. H. Beckett, A. R. Purkaystua, *J. Pharm. Pharmacol.* **27**, 31 P (1975).

[6] J. M. Lalancette, J. R. Brindle, *Can. J. Chem.* **48**, 735 (1970).

[7] For reviews, see: S. R. Sandler, W. Karo, *Organic Functional Group Preparations*, Vol. 3, Chapter 10, Academic Press, New York, 1972
J. Keck, *Methodicum Chimicum* Vol. 6, Chapter 3, F. Korte, Ed., Georg Thieme Verlag, Stuttgart, 1974.

[8] A. H. Beckett, R. T. Coutts, F. A. Ogunbona, *Tetrahedron* **29**, 4189 (1973).

[9] A. H. Beckett, K. Haya, G. R. Jones, P. H. Morgan, *Tetrahedron* **31**, 1531 (1975).

[10] A. C. Cope, T. T. Foster, P. H. Towle, *J. Am. Chem. Soc.* **71**, 3929 (1949).

[11] A. C. Cope, H. H. Lee, *J. Am. Chem. Soc.* **79**, 964 (1957).

Reactions of Sodium Borohydride in Acidic Media; VI. Reduction of Indoles with Cyanoborohydride in Acetic Acid[1]

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In 1974 we reported that indoles are converted to *N*-alkylindolines by the action of sodium borohydride in neat carboxylic acids[2]. During the course of that work we noted that sodium cyanoborohydride in acetic acid effected the reduction of the indole double bond without *N*-alkylation. We have since investigated this reduction with a variety of indoles and now wish to report our results.

The reaction of indoles **1** with sodium cyanoborohydride in glacial acetic acid proceeds rapidly at 15° to afford indolines **2** in excellent yield. Our results are tabulated in the Table.

1   NaCNBH₃ / CH₃COOH, 15°   **2**
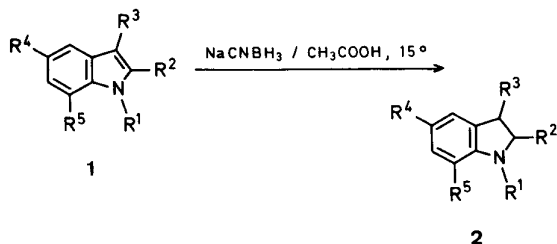
The reduction is general for alkyl-substituted indoles and tetrahydrocarbazoles and gives consistently higher yields of indolines than any of the previous indole reduction methods[3‑12]. The present method avoids the strongly acidic conditions characteristic of the dissolving metal reductions[3, 9‑12] (often leading to polymerization[13, 14, 15] of the indole) and avoids the extreme conditions[16] and hydrogenation equipment characteristic of catalytic reductions[3, 5, 6, 7] (which can lead to overreduction or result in unfavorable equilibria and low yields). Although improvements in both methods have been described[5, 11] neither the dissolving metal method nor the catalytic method of indole reduction have proven to be of general utility. Likewise, the method utilizing diborane[4] gives erratic yields of indolines and cannot be applied to *N*-substituted indoles. Only the method developed by Berger[8], using trimethylamine/borane in acid, approaches

the present indole reduction method in generality, convenience, and efficiency.

The reduction of indole (**1a**) to indoline (**2a**) by sodium cyanoborohydride in acetic acid appears to be complete in less than five mintes at 15° by G.L.C. analysis of the reaction mixture. Since we have previously shown that acetic acid protonates indoles at the 3-position[2], the reduction undoubtedly proceeds via the indolenium ion and reduction of this iminium ion by a cyanoborohydride species.

The method is clearly restricted to those indoles which are sufficiently basic to be protonated by acetic acid and, therefore, it is not surprising that 5-nitroindole and 2,3-diphenylindole fail to undergo reduction under these conditions (98% and 73% recovery, respectively). However, 3-methylindole (**1c**), which is much less basic than indole and 2-methylindole[17], undergoes smooth reduction to **2c**. The stronger acid trifluoroacetic acid has been used with sodium borohydride by us[2] and with sodium cyanoborohydride by Berger[18] to reduce the indole double bond in compounds containing a basic nitrogen (e. g., indoloquinolizidines[2]).

Although we have not observed polymerization of indoles in acetic acid under these conditions, some of the indolines, especially those with a 3-alkyl substituent (**2c**, **2l**), are air sensitive and rapidly darken after isolation, reverting in part to starting material.

The sodium cyanoborohydride/acetic acid reductions of *N*-unsubstituted indoles are carried out at 15° for 2 h to eliminate the possibility of *N*-ethylation[2], a reaction that does occur to a small extent (<10%) at higher temperatures and longer reaction times. The reductions of *N*-substituted indoles can be carried out at room temperature, but, of course with these indoles where *N*-alkylation is precluded, one can employ sodium borohydride in acetic acid[2].

General Procedure for Reduction of Indoles 1:

To a magnetically stirred solution of an indole (11.4 mmol) in glacial acetic acid (30 ml) at 15–17° under nitrogen in a hood is added in one portion sodium cyanoborohydride (Ventron, technical grade; 35 mmol). The mixture is stirred at 15° for 2 h. Water (150 ml) is then added and the mixture is cooled in an ice bath and slowly made strongly basic with sodium hydroxide pellets. The mixture is extracted with ether (4 × 75 ml). The ether extract is washed with water (2 × 100 ml) and brine (2 × 100 ml), dried over anhydrous potassium carbonate, and concentrated in vacuo to give the crude indoline, generally as a pale yellow oil and usually homogeneous by T.L.C. (benzene or ethyl acetate/triethylamine, 95/5). Distillation (or recrystallization) affords the pure indoline, generally as a colorless oil, in the yield and with the boiling point shown in the Table. Indolines are identified by I.R. and ¹H-N.M.R., and, where possible, by direct comparison with previously prepared[2] or commerical samples.

To minimize oxidation of the indoline, the reaction and workup should be carried out in one day; this is particularly important for 3-alkyl- and 1,3-dialkylindolines which appear to oxidize rapidly. If necessary, any indole contaminant can be removed by extracting the ether extract with dilute hydrochloric acid, basifying, and extracting with ether to recover the indoline.