grade). The predominant isomer **3** crystallized slowly after seeding by chilling to −75° and was recrystallized from cold pentane with 50% recovery. The analytical sample of **3** was further recrystallized and sublimed: mp 66–69°; nmr (CCl_4) δ 3.03 (d, 1, J = 9 Hz, 0.5CH_2), 3.14 (d, 1, J = 7, 0.5CH_2), with satellites 14 and 22 Hz each side of the center of gravity of the foregoing two doublets, δ 4.68 (subdivided t, 1, J = 7, 9, and ~1.4 Hz, CHBr), 6.04–6.06 (2 d partially resolved, 2, J = 1–2 Hz, weak satellites 12 Hz to each side, CH=CH); mass spectrum m/e 273 up to 278 (mol wt (calcd) 275 av, 278 max), base peak 195 ($C_6H_{15}{}^{11}B_8{}^{10}B_2$).

Anal. Calcd for $C_6H_{15}B_{10}Br$: C, 26.19; H, 5.49; B, 39.28; Br, 29.04. Found: C, 26.34; H, 5.96; B, 39.53; Br, 29.15.

The minor isomer **4** could not be isolated, but nmr peaks assigned include δ 3.43 (t or 2 d, $J \cong 2$, CH_2) and 5.15 (about five, peaks ~2 Hz spacing, CHBr), with other peaks obscured by other components of the mixture.

1-(*tert*-Butylamino)-1,4-dihydrobenzocarborane (5). *tert*-Butylamine (1 ml) was added to a solution of 1.07 g of crystalline 2-bromo-1,2-dihydrobenzocarborane (**3**) in 5 ml of ether at 25°. Crystals of *tert*-butylamine hydrobromide separated within 30 sec and were filtered after a few minutes. The filtrate was diluted with ether and pentane and washed with dilute aqueous sodium dihydrogen phosphate, then water. The ether–pentane solution was concentrated and the residue was chromatographed on alumina with cyclohexane, then sublimed twice: yield 0.57 g; mp 60–63°; nmr (CCl_4) δ 0.90 (broadened d, 1, J = 8 Hz, NH), 1.03 (s, 9, C(CH_3)$_3$), 2.90 (m, 2, $J \cong 2$, CH_2), 3.83 (d, 1, $J \cong 7$, width at half-height 16 Hz, N–CH), 5.60 (m, 2, $J \cong 2$, satellites 12 and 15 Hz each side, CH=CH); mass spectrum m/e 267 ($C_{10}H_{25}B_{10}N$), 252 (base peak, $C_9H_{22}{}^{11}B_8{}^{10}B_2N$ or $C_9H_{23}{}^{11}B_7{}^{10}B_3N$), 194 (benzocarborane), 125 (+2 charge from isotope pattern).

Anal. Calcd for $C_{10}H_{25}B_{10}N$: C, 44.91; H, 9.42; B, 40.43; N, 5.24. Found: C, 44.95; H, 9.37; B, 40.25; N, 5.16.

Benzocarborane (1) (95%, with 5% 2). A solution of 9.2 g of distilled bromodihydrobenzocarborane (mixture of **3** and **4**) in 100 ml of dimethylformamide was heated rapidly and refluxed 10 min, then cooled promptly. The solution was diluted with a few hundred milliliters of water and the benzocarborane was extracted with four 50-ml portions of pentane. The pentane solution was washed with water and concentrated to yield 5.5 g of residue, which was recrystallized from 45 ml of methanol and 6 ml of water, then sublimed: mp 111–118°; 3.96 g (61%) plus 0.5 g from mother liquor; mass spectrum m/e 194 ($C_6H_{14}{}^{11}B_8{}^{10}B_2$) with isotopic satellites; dihydrobenzocarborane (**2**) content 5% by nmr.

Benzocarborane Dibromide (6 and 7). A solution of 2.2 g of 95% benzocarborane and 1.85 g of bromine in 20 ml of methylene chloride was allowed to stand at 25° for 2.5 hr. (After 1 hr, nmr analysis showed no benzocarborane. Similar concentrations in carbon tetrachloride showed 50 mol % benzocarborane remaining after 1.2 hr.) Concentration under vacuum followed by crystallization from 4 ml of cyclohexane and 12 ml of pentane at −15° gave 1.6 g of benzocarborane dibromide (**6** and **7**, ~50:50 mixture, see Synthesis section for nmr data), second crop 0.9 g, 64%. The noncrystalline residue showed benzocarborane peaks in the nmr, as if some reversal of bromination had occurred. The analytical sample of the 50:50 mixture of **6** and **7** was recrystallized and survived slow vacuum sublimation at 40–50°, mp 75–90° dec (Br_2 evolution). The less soluble isomer (nmr singlets δ 4.8 and 6.0) was separated by slow crystallization from pentane, mp 125–128°.

Anal. Calcd for $C_6H_{14}B_{10}Br_2$: C, 20.35; H, 3.99; B, 30.53; Br, 45.13. Found (isomer mixture): C, 20.39; H, 4.01; B, 30.62; Br, 45.25; (less soluble isomer) C, 20.53; H, 4.21; B, 30.26; Br, 44.34.

Benzocarborane (1) from 6 and 7. A 1.2-g portion of recrystallized benzocarborane dibromide (**6** and **7**) was added to a solution of 4 g of sodium iodide in 10 ml of acetone. Immediate exothermic reaction and darkening occurred, but nmr analysis after 5 min indicated much remaining benzocarborane dibromide isomer characterized by doublets at δ 5.2 and 5.9, even though the other isomer had entirely disappeared. After 24 hr at 25°, a few milliliters of water was added and the benzocarborane was extracted into pentane and freed of iodine by repeated washing with concentrated aqueous sodium iodide. Crystallization from methanol–water followed by sublimation yielded 0.66 g of pure benzocarborane (**1**): mp 121–123° (capillary), 121.0, 121.3° (Mettler FP-1); see Figures 2 and 3 for uv and nmr spectra.

Anal. Calcd for $C_6H_{14}B_{10}$: C, 37.10; H, 7.26; B, 55.64. Found: C, 36.82; H, 7.41; B, 55.77.

Acknowledgment. D. S. M. thanks M. F. Hawthorne for helpful discussions and for the use of laboratory facilities during his sabbatical leave at the University of California, Riverside, 1969, where much of the experimental work reported here was completed.

The Cyanohydridoborate Anion as a Selective Reducing Agent

Richard F. Borch,*[1a] Mark D. Bernstein, and H. Dupont Durst[1b]

Contribution from the Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received September 8, 1970*

Abstract: Sodium cyanohydridoborate ($NaBH_3CN$) reduces a wide variety of organic functional groups with remarkable selectivity. The reduction of aldehydes and ketones is pH dependent, the reaction proceeding readily at pH 3–4. Oximes are smoothly reduced to alkylhydroxylamines and enamines are reduced to amines under acid catalysis. Reaction of an aldehyde or ketone with ammonia, primary amine, or secondary amine at pH ~7 in the presence of BH_3CN^- leads to primary, secondary, or tertiary amines, respectively, *via* reductive amination of the carbonyl group. Reaction of substituted pyruvic acids with ammonia and BH_3CN^- affords an excellent method for the synthesis of amino acids; ^{15}N labeling can be accomplished by using $^{15}NH_3$. The hydrogens of BH_3CN^- can be readily exchanged for either deuterium or tritium, thus permitting the synthesis of deuterium- or tritium-labeled alcohols, amines, and amino acids.

Considerable attention has been devoted to the study of modified boron hydrides as selective reducing agents for organic functional groups.[2,3] The earlier discovery of the reducing power[4] and the acid stability[5] of lithium cyanohydridoborate encour-

(1) (a) Alfred P. Sloan Foundation Fellow; (b) National Institutes of Health Predoctoral Fellow, 1968–1970. Taken in part from the Ph.D. Thesis of H. D. D., University of Minnesota, 1970.

(2) (a) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **78**, 2582 (1956); (b) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962); (c) R. Paul and N. Joseph, *Bull. Soc. Chem. Fr.*, 550 (1952); (d) H. C. Brown and E. J. Mead, *J. Amer. Chem. Soc.*, **75**, 6263 (1953).

(3) (a) H. Noth and H. Beyer, *Chem. Ber.*, **93**, 1078 (1960); (b) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **26**, 1437 (1961); (c) S. S. White, Jr., and H. C. Kelly, *J. Amer. Chem. Soc.*, **92**, 4203 (1970), and references therein.

(4) R. F. Borch and H. D. Durst, *ibid.*, **91**, 3996 (1969).

aged us to carry out an extensive investigation into the reducing properties of the cyanohydridoborate (BH_3CN^-) anion in organic systems.[6] The results of this study, described in this paper, demonstrate that cyanohydridoborate is indeed a versatile and remarkably selective reagent which should find extensive application in organic reductions.

Wittig first prepared BH_3CN^- as the lithium salt.[7] An early report[8] concerning its ability to reduce carbonyl groups indicated little promise for BH_3CN^- as a reducing agent, inasmuch as aldehydes were the only groups studied which were reduced. Fortuitously, our need for a reagent to reduce imines under acidic conditions coincided with Kreevoy's finding[5] that BH_3CN^- was stable in acid down to pH ~3. We subsequently found (*vide infra*) that the BH_3CN^- reduction of aldehydes, ketones, and imines is pH dependent, and that proper control of pH provided an excellent means for selective control of competing reactions. In most of the work described below, $NaBH_3CN$[9] and $LiBH_3CN$ were used interchangeably; no differences in reactivity were observed.

Results and Discussion

Purification and Modification of $NaBH_3CN$. For most of the reactions described below, the purity of the commercially available material[9] is adequate. If desired, however, the material may be further purified by recrystallization of its dioxane complex. The dioxane complex is a poor reducing agent in organic solvents as a result of its incomplete dissociation in all but aqueous systems. Therefore, $NaBH_3CN$ is liberated from the complex by heating *in vacuo*, affording a hygroscopic powder which is >98% pure $NaBH_3CN$. The hydrogens in BH_3CN^- may be readily exchanged for either deuterium or tritium; since $k_2^{exch} \sim 15k_2^{hydr}$,[5] some loss of reagent due to hydrolysis will occur. Tritium can be readily incorporated by stirring the reagent at pH ~3 in $H_2{}^*O$; this solution may be used for reduction directly, or the $NaBH_3{}^*CN$ may be isolated and purified as above. Preparation of $NaBD_3CN$ (>95% D) was readily accomplished by cycling the material through two fresh batches of D_2O for four exchange half-lives each at pH ~2.

Reduction of Aldehydes and Ketones. Under neutral conditions in water or methanol negligible reduction of aldehydes and ketones was observed. As the pH is lowered, however, the reduction becomes progressively more rapid; at pH 3–4, the reduction rate is sufficiently rapid to be synthetically useful for most aldehydes and ketones. The reduction may be run in any protic solvent, including water; for most reactions, methanol is most convenient. Because the reduction consumes acid (eq 1 below), it is necessary either to use a buffered system or to add acid to maintain the pH. We have found it most convenient to use bromocresol green or methyl orange as indicators to monitor the change in pH; methanolic HCl is then added to regenerate the appropriate indicator color (see Experimental Section). The rate of color change also gives a rough idea of how fast the reaction is proceeding.

The results are summarized in Table I. The more easily reducible groups—aldehydes and unhindered aliphatic ketones—are readily reduced at pH ~4; for aromatic and hindered aliphatic ketones, it is necessary to go to pH ~3 to obtain complete reduction in a reasonable time. It was hoped that, because of the acidic conditions used for the reduction,[10] reaction of cyclopentenone with BH_3CN^- would afford mainly 2-cyclopenten-1-ol. Unfortunately, hydride addition at the β-carbon predominates, affording, as in the case of reduction with $NaBH_4$, cyclopentanol as the major product.

Table I. Reduction of Aldehydes and Ketones with $NaBH_3CN$ in Methanol at 25°

Compound	Approximate pH[a]	Time, hr	Product	Yield, %
Farnesal	4	1	Farnesol	92
Farnesal	4	1	Farnesol-t_1[b]	86
PhCHO	4	2	$PhCH_2OH$	87
Cyclohexanone	4	1	Cyclohexanol	88
2-Heptanone	4	4	2-Heptanol	84
Pinacolone	3	2	$(CH_3)_3CH(OH)CH_3$	86
$PhCOCH_3$	3	1	$PhCH(OH)CH_3$	93
Ph_2CO	3	14	Ph_2CHOH	70
	4	1		67

[a] For "pH 4" reactions, bromocresol green was added and the pH was held at the yellow-green transition point by addition of methanolic HCl; for "pH 3" reactions, methyl orange was added and the pH was similarly held at the red-orange transition point. [b] Carried out using $NaBH_3{}^*CN$. Farnesol labeled >95% at C-1.

Reductions with tritium-labeled BH_3CN^- are generally carried out as above. Because of possible exchange between BD_3CN^- and methanol at the pH's employed for the reduction, however, deuterations are carried out in THF containing *ca.* 5% D_2O (to provide a proton source so that the indicator will function). The pH is maintained by addition of a solution of DCl–DOAc in D_2O–THF (prepared by addition of acetyl chloride to a D_2O–THF solution). The results are summarized in Table II.

Table II. Reduction of Selected Aldehydes and Ketones with $NaBD_3CN$ in THF–D_2O at 25°

Compound	Approximate pH[a]	Time, hr	Product[b]	Alcohol yield, %
PhCHO	4	4	PhCH(OH)D	85
$PhCOCH_3$	3	1	$PhCD(OH)CH_3$	88
Ph_2CO	3	24	$Ph_2C(OH)D$	67
Pinacolone	3	2	$(CH_3)_3CCD(OH)CH_3$	84

[a] Maintained as in footnote *a*, Table I, except that acid solution was DOAc–DCl in D_2O–THF. [b] All alcohols were 95 ± 2% D_1 by nmr and mass spectral analysis.

(5) M. M. Kreevoy and J. E. C. Hutchins, *J. Amer. Chem. Soc.*, **91**, 4329 (1969).

(6) The spectroscopic and chemical properties of the cyanohydridoborate anion have recently been reported: J. R. Berschied, Jr., and K. F. Purcell, *Inorg. Chem.*, **9**, 624 (1970).

(7) G. Wittig, *Justus Liebigs Ann. Chem.*, **573**, 209 (1951).

(8) G. Drefahl and E. Keil, *J. Prakt. Chem.*, **6**, 80 (1958).

(9) Available as sodium cyanoborohydride from Alfa Inorganics.

(10) Reduction of cyclopentenone with most hydride reducing agents is initiated by a Michael-type attack of hydride at the β-carbon, leading ultimately to the saturated alcohol as the major product. See H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969), and references cited therein.

Mechanism of Aldehyde and Ketone Reduction. The reaction is third order overall, first order each in ketone, BH_3CN^-, and hydrogen ion. Unlike the electronically analogous amine–boranes, which exhibit both acid-dependent and acid-independent pathways below pH 5,[11] BH_3CN^- exhibits only acid-dependent kinetics up to at least pH 6. Figure 1 shows the hydronium ion dependence of reduction for cyclohexanone; good first-order dependence is observed. That the hydrogen which is appended to the hydroxyl carbon comes from the reagent is confirmed by the fact that reduction of isobutyraldehyde with $NaBD_3CN$ in H_2O gives the deuterated alcohol. Finally, reaction of $NaBH_3CN$ with a large excess of cyclohexanone demonstrated that >2.9 hydride equiv is consumed per equiv of BH_3CN^-.

The results of the isotope-effect studies are not definitive. For the reduction of cyclohexanone in water, a negligible substrate isotope effect (1.03) and a large *inverse* solvent isotope effect ($k_2(D_2O)/k_2(H_2O)$ = 2.3) were observed.[12] The small substrate isotope effect cannot be unambiguously explained, since it could be the product of a primary isotope effect and a significant inverse secondary isotope effect.[13] The inverse solvent isotope effect is quite close to that observed by White and Kelly[11] for the reduction of acetone by morpholine–borane ($k_2(D_2O)/k_2(H_2O)$ = 2.8).

On the basis of these results, we propose a mechanism for this reduction analogous to that proposed[11] for the morpholine–borane reduction as shown in eq 2. The direction of the solvent isotope effect strongly supports an initial reversible protonation of the carbonyl group followed by rate-determining hydride transfer to the protonated species. Prior preequilibrium protonation of BH_3CN^- can be ruled out since reduction competes very successfully with hydrolysis (and exchange). It is interesting to note that, in spite of the apparent parallel in reaction mechanism, 1 equiv of BH_3CN^- uses 2.9 equiv of hydride for reduction whereas morpholine–borane uses only 1.1 equiv for reduction at the same initial ketone concentration. Thus, the carbonyl group catalyzes morpholine–borane hydrolysis to a significant extent, whereas this catalysis is negligible for BH_3CN^- hydrolysis during the reduction of cyclohexanone at pH ~4.

$$3\ \text{C=O} + BH_3CN^- + H^+ + ROH \longrightarrow 3HCOH + B(OR)_3 + HCN \quad (1)$$

$$\text{C=O} + H_3{}^+O \rightleftharpoons \left[\text{C=OH}\right]^+ + BH_3CN^- \xrightarrow{\text{r.d.}} HCOH \quad (2)$$

Reduction of Oximes. The reduction of ketoximes at pH ~4 proceeds smoothly to the corresponding *N*-alkylhydroxylamines; no trace of overreduction to the amine was observed. When aldoximes were reduced under these conditions, however, the major product was the dialkylhydroxylamine; presumably this occurs as shown in eq 3. The reduction of oximes is also pH dependent, and it appeared likely that, if the pH were lowered sufficiently to cause *very* rapid reduction of the oxime, the second step in eq 3 would be diminished in favor of the first step. This indeed turned out to be the case; when the pH was lowered to 3, the aldoximes were rapidly reduced to give the monoalkylhydroxylamine as the major product. The results are summarized in Table III.

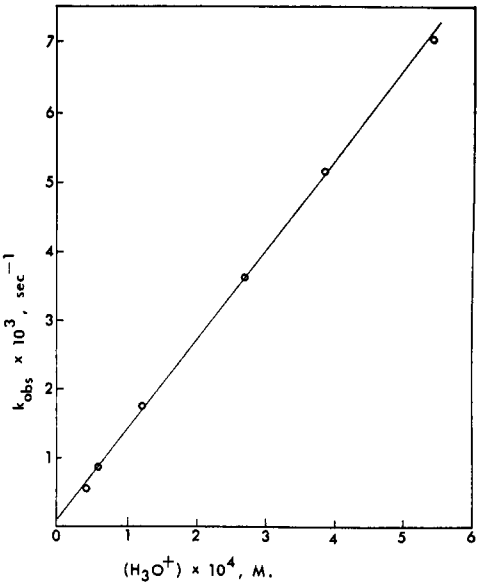


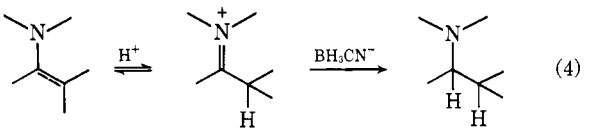
Figure 1. Hydronium ion dependence of the rate of reduction of cyclohexanone by $NaBH_3CH$ in water at 25°.

$$RCH{=}NOH \xrightarrow[H^+]{BH_3CN^-} RCH_2\ddot{N}HOH + RCH{=}NOH \longrightarrow \xrightarrow{-H^+}$$

$$RCH_2\overset{\overset{OH}{|}}{N}{-}CHNHOH \longrightarrow \quad (R,\ -H^+)$$

$$H_2NOH + RCH_2\overset{\overset{OH}{|}}{\overset{+}{N}}{=}CHR \xrightarrow{BH_3CN^-} RCH_2\overset{\overset{OH}{|}}{N}CH_2R \quad (3)$$

Reduction of Enamines. Because of the demonstrated propensity for BH_3CN^- to reduce imminium systems such as those derived from ketones and secondary amines[4] (*vide infra*), the enamine system appeared to be a likely candidate for reduction in acidic medium. Although the enamine group itself should be resistant to reduction, rapid (and reversible) protonation on carbon would generate a readily reducible imminium salt (eq 4). When the morpholine enamine of cyclohexanone was dissolved in absolute methanol–THF and allowed to react with BH_3CN^-, only a trace of



(4)

(11) S. S. White, Jr., and H. C. Kelly, *J. Amer. Chem. Soc.*, **92**, 4203 (1970), and references cited therein.

(12) The "substantial isotope effect" which we erroneously reported previously[4] was in fact due to the H^+ dependence of which we were unaware at that time.

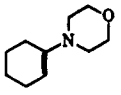
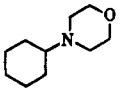
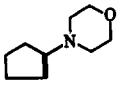
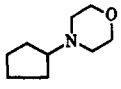
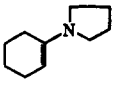
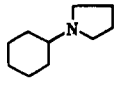
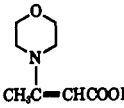
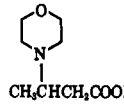
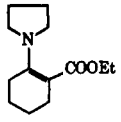
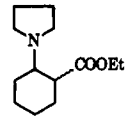
(13) An inverse isotope effect has been found in the hydrolysis of BH_4^- anion: see R. E. Davis, C. L. Kibby, and C. G. Swain *J. Amer. Chem. Soc.*, **82**, 5950 (1960).

Table III. Reduction of Oximes with $NaBH_3CN$ in Methanol at 25°

Oxime	Approximate pH[a]	Time, hr	Product	Mp, °C	Lit. mp, °C	Yield, %
	4	3		138–139	138–140[b]	66
	4	3		95–96	92–93[c]	77
	4			64–65	67[b]	73
	3	1		69–70[e]	91[d]	75
$PhCH{=}NOH$	4	4	$(PhCH_2)_2NOH$	118–119	123[f]	60
$PhCH{=}NOH$	3	1	$PhCH_2NHOH$	58–59	57[b]	79
$n\text{-}C_6H_{13}CH{=}NOH$	4	3	$(n\text{-}C_7H_{15})_2NOH$	72–73	74[f]	57
$n\text{-}C_6H_{13}CH{=}NOH$	3	1	$n\text{-}C_7H_{15}NHOH$	60–61	62[b]	53

[a] See footnote *a*, Table I. [b] H. Feuer and B. F. Vincent, Jr., *J. Amer. Chem. Soc.*, **84**, 3771 (1962). [c] Reference 16. [d] H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965). [e] Satisfactory spectral and analytical data were obtained for this compound; the reason for the melting point discrepancy is not clear. [f] G. Vavon and E. Krajcinovic, *Bull. Soc. Chim. Fr.*, [4] **43**, 231 (1968).

Table IV. Reduction of Enamines with $NaBH_3CN$ in THF–Methanol at 25°

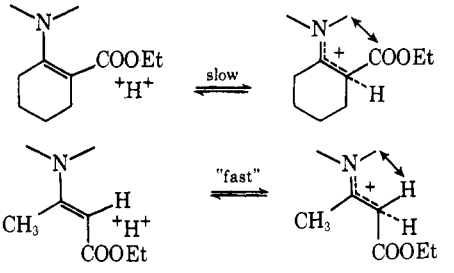
Compound	Time, hr	Product[a]	Yield, %	Picrate mp, °C
	0.2		80	176-177
	0.5		81	159-162
	0.5		86	167-169
	1[b]		65	124-126
	24[b]		50	

[a] Satisfactory spectral data and elemental analyses (on picrates) were obtained for all new compounds. [b] Reaction carried out in methanol at pH ~4.

reduction had occurred after 3 hr. When this experiment was repeated using the enamine hydrochloride, however, *quantitative reduction to the amine was complete in 15 min.* Thus, simple enamines are rapidly reduced by BH_3CN^- at an initial pH of 5; there is no need to hold the pH constant during the course of the reaction, since the initial reversible C protonation occurs at pH up to ~8, and therefore only a catalytic amount of acid is required. The 15:1 THF–methanol solvent mixture is used to minimize enamine hydrolysis as compared with methanol itself.

If the enamine is conjugated with a carbonyl group, thus giving it the properties of a vinylogous amide, reduction becomes more difficult as expected. Enamines derived from β-keto esters can be reduced in methanol providing that acid is added to hold the pH ~4 (see Table IV). Because of the decreased basicity of these conjugated enamines, stronger acid is required for the initial protonation step. Enamines derived from β-diketones, however, are resistant to reduction. The morpholine enamine of dimedone, for example, was recovered unchanged after reaction with BH_3CN^- in methanol for 24 hr. The results are summarized in Table IV.

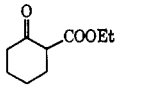
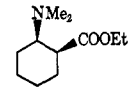
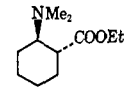
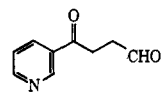
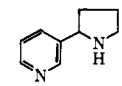
It is interesting to note the difference in reactivity between the two enamines in Table IV derived from β-keto esters. We attribute this decreased reactivity of the cyclic compound to an increase in steric crowding as protonation on carbon (and hence increasing the double bond character of the carbon–nitrogen bond) begins. In the acyclic system, however, the presence of a hydrogen cis to the amino group has minimal steric effect and allows protonation to proceed more rapidly.



Reductive Amination of Aldehydes and Ketones. Once we had established that reduction of the iminium moiety (*i.e.*, $>C{=}N^+R_2$ or $>C{=}N^+HR$) with BH_3CN^- was rapid at pH 6–7, and that reduction of aldehydes and ketones was negligible in this pH range, we realized the potential for BH_3CN^- to trap by reduction an imminium group in the presence of an aldehyde or ketone. The initial equilibrium step shown in eq 5 is known[14] to be unfavorable (*i.e.*, lies to the left) in most cases; fortuitously, however, the optimum pH for imminium formation is ~6. Thus, it

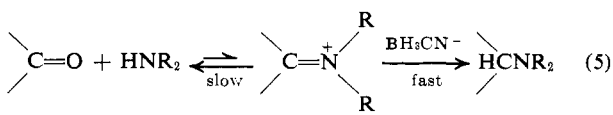
(14) The formation of the imminium system is a complex multistep process; for simplification we will treat it as a single transformation. See J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89**, 2669 (1967), and references therein.

Table V. Representative Reduction Aminations with $NaBH_3CN$ in Absolute Methanol (pH 6–8) at 25°

Compound	Amine	Product	Derivative mp, °C[a]	Yield, %[b] Anal.	Yield, %[b] Isol
Cyclohexanone	NH_3	Cyclohexylamine	204–204[c]	61	45
Cyclohexanone	CH_3NH_2	*N*-Methylcyclohexylamine	195–196[c]	50	41
Cyclohexanone	CH_3NHCH_3	*N,N*-Dimethylcyclohexylamine	177–180[d]	63	43
Cyclohexanone	CH_3NHCH_3	*N,N*-Dimethylcyclohexylamine	177–180[d]	90[j]	71[j]
Cyclohexanone	Morpholine	*N*-Cyclohexylmorpholine	175–176[d]	85	79
Norbornanone	NH_3	*endo*-Norbornylamine	256–258[c]	63	48
Norbornanone	CH_3NHCH_3	*N,N*-Dimethylnorbornylamine	219[d]	29	
Norbornanone	CH_3NHCH_3	*N,N*-Dimethylnorbornylamine	219[d]	88[j]	47[j]
Cycloheptanone	CH_3NH_2	*N*-Methylcycloheptylamine	264–265[e]	76	61
Cycloheptanone	CH_3NHCH_3	*N,N*-Dimethylcycloheptylamine	188–189[d]	78	63
Cyclooctanone	CH_3NH_2	*N*-Methylcyclooctylamine	273–275[e]	75	56
Cyclooctanone	CH_3NHCH_3	*N,N*-Dimethylcyclooctylamine	198–200[d]	72	59
Cyclooctanone	$(CH_3)_2CHCH_2NH_2$	Isobutylcyclooctylamine	182–183[c]		79
Acetophenone	NH_3	α-Phenylethylamine	156–156[c]	86	77
Acetophenone	CH_3NH_2	*N*-Methylphenethylamine	178–179[c]	95	78
Acetophenone	NH_3	$(PhCHCH_3)_2NH$[i]		41	
		$PhCH(CH_3)NH_2$		22	
Isobutyrophenone	NH_3	1-Phenylisobutylamine	281–282[c]	75	59
Isobutyrophenone	CH_3NH_2	Methyl-1-phenylisobutylamine	176–177[c]	91	90
Isobutyrophenone	CH_3NHCH_3	Dimethyl-1-phenylisobutylamine		5	
Cyclopentanone	CH_3NHCH_3	*N,N*-Dimethylcyclopentylamine	175–178[d]		57
Cyclopentanone	H_2NOH	*N*-Cyclopentylhydroxylamine	94–96[f]		66[f]
2-Butanone	H_2NOH	*N*-(2-Butyl)hydroxylamine	64–65[f]		64[f]
4-Nonanone	CH_3NHCH_3	4-(*N,N*-Dimethylamino)nonane	215–216[e]	90	77
Benzaldehyde	$CH_3CH_2NH_2$	*N*-Ethylbenzylamine	183[c]	91	80
3,4-Dimethoxybenzaldehyde	CH_3NH_2	*N*-Methyl-3,4-dimethoxybenzylamine	205–207[c]	60	51
3,4-Dimethoxybenzaldehyde	CH_3NHCH_3	*N,N*-Dimethyl-3,4-dimethoxybenzylamine	207–208[c]	80	59
Isobutyraldehyde	$PhNH_2$	*N*-Isobutylaniline		95	78
	CH_3NHCH_3	 + 	116–118[d]		21 + 32
Acetophenone	CH_3NH_2	$PhC(CH_3)NHCH_3$[g] (D)	177–180[c]	97	72
Glutaraldehyde	CH_3NH_2	*N*-Methylpiperidine	147–149[d]		43
	NH_3				47[h]

[a] All values are in accord with published literature values. [b] Analytical yield represents yield of crude oil, shown to be >95% pure by glpc; isolated yields represent recrystallized solid derivative. [c] Hydrochloride. [d] Picrate. [e] Methiodide. [f] Melting point of the compound itself. Compound isolated as a crystalline solid, not as a derivative. [g] $NaBD_3CN$ used as the reducing agent. [h] We are grateful to Dr. H. V. Isaacson for making his results available to us. [i] A threefold excess of acetophenone was used. [j] Reaction carried out in the presence of Linde 3A molecular sieves.

was conceivable that an aldehyde or ketone could be reductively aminated by simply reacting the carbonyl compound with amine at pH ~6 in the presence of BH_3CN^-.



(5)

Our expectations were realized when, after stirring cyclohexanone, *n*-propylamine, and lithium cyanohydridoborate in methanol for 24 hr, we isolated an 85% yield of *n*-propylcyclohexylamine. The reaction is general for ammonia and primary and secondary aliphatic amines; aromatic amines are somewhat sluggish presumably due to slower imine formation. All aldehydes and relatively unhindered ketones may serve as carbonyl sources; hindered ketones (*e.g.*, pinacolone) and diaryl ketones will not react. For example, acetophenone, isobutyrophenone, and phenyl *tert*-butyl ketone are reductively aminated with dimethylamine in 92, <5, and <1% yield, respectively. Since these latter ketones themselves reduce with BH_3CN^-, the initial imine formation step is probably the source of difficulty. Although pH 6–8 is optimum for reductive aminations, we have successfully exploited these reactions at pH's as low as 4 and as high as 10. The only requirement appears to be the presence of enough proton source to generate a positively charged $>C{=}^+N<$ moiety. Finally, the use of 3A molecular sieves to absorb the water generated in the reaction causes a definite improvement in yield and is par-

ticularly useful for those ketones (*e.g.*, norbornanone) which form imines slowly. The results are summarized in Table V.

As in the reduction of carbonyl groups, all three BH_3CN^- hydrides are utilized. The reductive aminations are usually run using a fivefold excess of the amine; although this improves the initial equilibrium in eq 5, the main purpose is to prevent the product amine (when primary or secondary) from undergoing further reaction with the carbonyl compound. For example, when acetophenone is treated with a fivefold excess of ammonia at pH 6 in the presence of BH_3CN^-, α-phenethylamine is obtained in 74% yield. When only 1 equiv of ammonia is used, however, di(α,α'-phenethyl)amine is obtained as the major product. We propose a mechanism for the reductive amination as shown in eq 5, where a slow (and rate-determining) preequilibrium step generates the imminium moiety which is then rapidly reduced to product. The results of the enamine reductions argue against a rate-determining hydride-transfer step, since the same imminium moiety is generated in both cases (*vide supra*), but the enamine reduction is complete in 15 min *vs.* 18–36 hr for the reductive amination. Thus both reactions presumably go through the same intermediate, but the enamine forms the intermediate by rapid reversible protonation and the ketone forms it by a slow multistep sequence *via* the carbinolamine.

The substituted pyruvic acids constitute a special case of reductive amination, since the products from this reaction are α-amino acids. Two special features make these reactions unique. First, because of the lability of the pyruvic acid carbonyl (especially in base), side reactions are more prevalent, and pH control is more crucial. For example, reductive amination of 3-indolylpyruvic acid with ammonia at pH 9 afforded only polymeric material, while at pH 7 a 37% yield of tryptophan was obtained. Thus, preparation of amino acids should be carried out as close to pH 7 as possible. This unusual reactivity of the α-keto acid carbonyl also permits reductive aminations to be carried out in aqueous medium, although the yields are generally somewhat lower than in methanol. Second, the poor nucleophilicity of the amino group in an α-amino acid results in a low degree of reactivity for the product amine, and therefore the product will not react further with the starting carbonyl compound. Hence, amino acids can be prepared (albeit in reduced yield) by using the amine as the limiting reagent. This is the most efficient and economical route available for preparing ^{15}N-labeled amino acids. The results are summarized in Table VI.

In principle, any carbon–oxygen or carbon–nitrogen multiple bond which can be sufficiently polarized in acid should be reducible with cyanohydridoborate anion. We have studied two functional groups—the amide and the nitrile—extensively, since it is known that both of these groups can be protonated in strong acid. In both cases, however, we observed no evidence of reduction. Apparently the extent of protonation of either nitrile or amide at pH 2 (the lowest useful pH for BH_3CN^- reactions) is still insufficient to promote reduction. Similarly, esters, acids, and lactones are inert to the reagent. Acid chlorides are smoothly reduced to the corresponding alcohols in tetrahydrofuran;[15] attempts to stop the reduction at the aldehyde stage, however, were unsuccessful. Finally, we have observed reduction of some pyridinium compounds with BH_3CN^-; at present, however, the results are complex and appear to depend on ring substitution. Complete understanding of this reduction must await further investigation.

Table VI. Reductive Amination of Substituted Pyruvic Acids with $NaBH_3CN$ in Absolute Methanol (pH 6–8)[a] at 25°. Synthesis of Amino Acids

Keto acid	Amino acid	Yield, %
Glyoxylic	Glycine	52
Pyruvic	Alanine	50
2-Oxoglutaric	Glutamic acid	51
p-Hydroxyphenylpyruvic	Tyrosine	46
3-Indolylpyruvic	Tryptophan	37
3-Indolylpyruvic	Tryptophan-^{15}N[b]	23
Phenylpyruvic	Phenylalanine	49
Phenylpyruvic	Phenylalanine-*2-t*[c]	47

[a] pH adjusted until no change of color was observed on either red or blue litmus. See Experimental Section. [b] Carried out using 1.2 equiv of >95% $^{15}NH_4NO_3$. Tryptophan obtained labeled >94% ^{15}N at C-2. We are grateful to Dr. D. McMinn for making his results available to us. [c] Carried out using $NaBH_3{}^*CN$. Phenylalanine obtained had activity of 10^5 dpm.

It should be noted that both the imine reduction and the reductive amination reactions serve as *in vitro* models for pyridoxal phosphate–pyridoxamine type transamination reactions *in vivo*. The fact that cyanohydridoborate is stable in aqueous systems at pH 7, readily reduces imines, and aminates α-keto acids under these conditions generates excellent opportunities for carrying out reductions and aminations on complex biological systems.

Experimental Section

General Comments. $NaBH_3CN$ was obtained from Alfa Inorganics and was generally used without purification. Glpc analyses were carried out on either a Varian Aerograph Model 90-P or Model 204 gas chromatograph. Tritiated water (1 Ci/ml) was obtained from Tracerlabs, Waltham, Mass., and was diluted prior to use. D_2O (99.8% D) was obtained from Stohler Isotope Chemicals. Radioactivity measurements were carried out in a Nuclear Chicago Model 724 liquid scintillation system using dioxane–water as solvent. Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were determined by the Microanalysis Laboratory, University of Minnesota.

Purification of $NaBH_3CN$. Sodium cyanohydridoborate (10 g) was dissolved in 80 ml of tetrahydrofuran, and 1 *M* HCl–methanol was added until 1 drop of the solution showed pH ~9 on pH paper. The solution was then poured with stirring into 250 ml of dioxane. The precipitate was filtered, and the wet solid was stirred for 2 hr in 250 ml of ethyl acetate This solution was then filtered *in vacuo* through Hy-Flo and heated to reflux on the steam bath; then 150 ml of dioxane was added in portions with swirling This solution was slowly cooled to room temperature, then chilled and filtered. The crystalline dioxane complex was dried *in vacuo* for 4 hr at room temperature, then for 4 hr at 80°. The resulting amorphous hydroscopic powder (6.74 g) was >98% $NaBH_3CN$ by iodometric titration.[5]

Preparation of $NaBD_3CN$. A 50-ml three-necked flask equipped with an addition funnel, a magnetic stirrer, and a combination electrode connected to a pH meter was charged with 2 g of commercial $NaBH_3CN$ and 15 ml of 99+% D_2O. The addition funnel was charged with a solution of ACOD–DCl in D_2O (prepared by *cautious* addition of 0.8 ml of acetyl chloride to 4 ml of D_2O). The acid solution was added to the stirred reaction mixture at a rate sufficient to bring the pH to 2, then added at such a rate that the pH

(15) C. V. Grudzinskas, private communication.

was held at 1.8–2.2 for 30 min. Anhydrous sodium carbonate was added until pH ~6, and the D_2O was removed at reduced pressure (this D_2O, which contains only *ca.* 5% H, can be recycled in the first exchange subsequent runs). The residue was dissolved in 12 ml of fresh D_2O, and the solution was maintained at pH 1.8–2.2 for 30 min. After neutralization and removal of the D_2O, the solid residue was vigorously stirred for 1 hr with 25 ml of THF; this suspension was filtered and the THF evaporated to give 1.2 g of crude $NaBD_3CN$. Ir and nmr analyses indicated that this material was >95% deuterated. If desired, this material can be purified as described above, adjusting the quantities of solvents accordingly.

Preparation of $NaBH_3CN$-*t*. A trace of methyl orange was added to a solution of 1.1 g of $NaBH_3CN$ in 10 ml of water which contained 100 mCi of tritium. The resulting solution was maintained at the red color (pH ~3) for 30 min by dropwise addition of 0.2 *N* HCl. Solid Na_2CO_3 was added until pH ~7 (pH paper), and the solution was evaporated to dryness *in vacuo*. The solid residue was stirred overnight with 50 ml of THF and filtered. The resulting solution was evaporated *in vacuo* to give 750 mg of product, which showed a specific activity of 49.5 μCi/mmol.

Reduction of Aldehydes and Ketones. Procedure A. The reduction of cyclohexanone is typical of the pH ~4 reductions. Cyclohexanone (390 mg, 4 mmol) and a trace of bromocresol green were dissolved in 6 ml of methanol, and 125 mg (2 mmol, 6 mequiv H^-) of $NaBH_3CN$ was added. The solution immediately turned deep blue, and 2 *N* HCl–methanol was added dropwise with stirring to restore the yellow color. After *ca.* 10 min, the color changed very slowly. The solution was stirred an additional 50 min, 1 drop of acid being added occasionally to restore the yellow color. The methanol was evaporated at reduced pressure, and the residue was taken up in 5 ml of water, saturated with sodium chloride, and extracted with four 5-ml portions of ether. The combined extracts were dried ($MgSO_4$) and freed of solvent *in vacuo* to give 350 mg (88%) of gas chromatographically pure cyclohexanol, identified by infrared spectrum and glpc peak enhancement with an authentic sample.

Procedure B. The reduction of acetophenone is typical of the pH ~3 reductions. Acetophenone (450 mg, 3.75 mmol) and $NaBH_3CN$ (250 mg, 4 mmol) were dissolved in 5 ml of methanol. A trace of methyl orange was added, and 2 *N* HCl–methanol was added dropwise with stirring to maintain the red color. After *ca.* 15 min, the color changed very slowly. Stirring was continued for an additional 45 min, and the methanol was evaporated *in vacuo*. The residue was taken up in 5 ml of water, saturated with sodium chloride, and extracted with four 5-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated at reduced pressure to give 425 mg (93%) of colorless oil. Glpc analysis indicated that the product was >98% α-phenethanol containing <2% acetophenone, identified by ir, nmr, and glpc peak enhancement.

3,3-Dimethylbutan-2-ol-2-*d*. A trace of methyl orange was dissolved in 0.1 ml of D_2O and then added to 2 ml of THF. Pinacolone (300 mg, 3 mmol) and $NaBD_3CN$ (190 mg, 3 mmol) were added, and a solution of DCl–DOAc in THF (prepared by the addition of 0.3 ml of D_2O to 0.3 ml of acetyl chloride in 2 ml of THF) was added dropwise with stirring to maintain the red color. After *ca.* 5 min, the red color persisted; stirring was continued for 2 hr. The solution was poured into 100 ml of water, saturated with sodium chloride, and extracted with three 10-ml portion of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 265 mg (84%) of glpc pure alcohol. Nmr and mass spectral analysis indicated >96% deuterium incorporation.

Kinetics. Rate data were obtained spectrophotometrically at 275 nm using a Beckman DU spectrophotometer equipped with a water-jacketed cell compartment thermostated to 25.0 ± 1.0°. pH measurements were obtained with a Radiometer expanded scale pH meter. All reactions were run at $NaBH_3CN$ or $NaBD_3CN$ concentrations of 0.10 *M*, at total buffer concentration of 0.30 *M*, and the ionic strength adjusted to 1.0 with sodium chloride before addition of the carbonyl compound. An acetic acid–sodium acetate buffer was used, and the solvent was either deionized water or D_2O (determinations in triple-distilled water and tap water indicated negligible catalysis by metal cations). Absorbances were measured at intervals such that approximately ten readings were taken during the first two half-lives; the infinity points were taken after 8–10 half-lives. Initial concentrations of carbonyl compound were on the order of 0.002–0.003 *M*.

Reduction of Oximes. The reduction of cyclopentanone oxime is typical. To a solution of cyclopentanone oxime (300 mg, 3 mmol) and $NaBH_3CN$ (125 mg, 2 mmol) in 3 ml of methanol was added a trace of bromocresol green. A solution of 2 *N* HCl–methanol was then added dropwise with stirring to maintain the yellow color. After *ca.* 15 min, the color changed very slowly. The solution was stirred for 3 hr, and the methanol was removed at reduced pressure. The residue was dissolved in 2 ml of water, raised to pH >9 with 6 *N* KOH, saturated with sodium chloride, and extracted with four 5-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 305 mg of solid. One recrystallization from petroleum ether afforded 236 mg of *N*-cyclopentylhydroxylamine, mp 95–96° (lit.[16] mp 92–93°).

Reduction of Enamines. Procedure A. To a solution of 1-morpholino-1-cyclopentene (500 mg, 3.25 mmol) in 12 ml of THF was added gaseous HCl until precipitation of the enamine hydrochloride was complete. To this suspension was added a solution of 130 mg (2 mmol) of $NaBH_3CN$ in 3 ml of absolute methanol in one portion with stirring. The resulting solution was stirred 30 min at 25°, then freed of solvent *in vacuo* and taken up in 10 ml of 0.1 *N* KOH. The aqueous suspension was extracted with three 10-ml portions of ether, and the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 410 mg (81%) of glpc homogeneous product, identical with an authentic sample of *N*-cyclopentylmorpholine by glpc peak enhancement, ir, and mixture melting point of picrates; picrate mp 159–162°.

Procedure B. To a solution of 400 mg (2 mmol) of ethyl 3-(*N*-morpholino)crotonate (prepared from morpholine and ethyl acetoacetate) in 4 ml of methanol at 25° was added a trace of bromocresol green. A 2 *N* HCl–methanol solution was added until the color turned yellow, and 130 mg (2 mmol) of $NaBH_3CN$ was added with stirring. The HCl–methanol solution was then added dropwise to maintain the yellow color. After *ca.* 5 min, the color changed very slowly. Stirring was continued at 25° for 1 hr. The solution was poured into 5 ml of 0.1 *N* NaOH, saturated with NaCl, and extracted with three 10-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 315 mg of crude product. Tlc analysis showed one major and two minor spots. The crude product was dissolved in 10 ml of 1 *N* hydrochloric acid and extracted with two 10-ml portions of ether. The aqueous solution was then brought to pH >9 with 6 *N* KOH, saturated with NaCl, and extracted with three 10-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 260 mg (65%) of chromatographically pure ethyl 3-(*N*-morpholino)butyrate, picrate mp 124–126°. *Anal.* Calcd for $C_{16}H_{22}N_4O_{10}$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.68; H, 5.11; N, 12.66.

Reductive Amination with Ammonia. Procedure A. The preparation of *endo*-norbornylamine is typical. A solution of 2-norbornanone (1.1 g, 10 mmol), ammonium acetate (7.7 g, 100 mmol), and $LiBH_3CN$ (330 mg, 7 mmol) in 30 ml of absolute methanol was stirred 48 hr at 25°. Concentrated HCl was added until pH <2, and the methanol was removed *in vacuo*. The residue was taken up in 10 ml of water and extracted with three 20-ml portions of ether. The aqueous solution was brought to pH >10 with solid KOH, saturated with NaCl, and extracted with five 15-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 700 mg (63%) of glpc pure *endo*-norbornylamine. The hydrochloride was prepared by dissolving the crude product in 10 ml of methanol, bubbling in HCl gas until pH <2, and evaporating to dryness. The crude hydrochloride was recrystallized from EtOH–EtOAc–cyclohexane to give 700 mg (48%) of hydrochloride, mp 256–258° (lit.[17] mp 255–265°).

Reductive Amination with Primary Amines. Procedure B. The preparation of *N*-methylcyclooctylamine is typical. To a solution of 1.9 g (60 mmol) of anhydrous methylamine in 25 ml of absolute methanol was added 4 ml (20 mmol) of 5 *N* HCl–methanol, followed by 1.26 g (10 mmol) of cyclooctanone and 300 mg (6 mmol) of $LiBH_3CN$. The solution was stirred at 25° for 72 hr, then worked up as in procedure A to give 1.04 g (75%) of glpc pure *N*-methylcyclooctylamine. Conversion to the hydrochloride as above afforded 973 mg (56%) of product, mp 144–147° (EtOAc–cyclohexane).

Reductive Amination with Secondary Amines. Procedure C. The preparation of *N*,*N*-dimethyl(α-phenethyl)amine is typical. To a solution of 2.7 g (60 mmol) of dimethylamine in 25 ml of methanol was added 4 ml (20 mmol) of 5 *N* HCl–methanol, fol-

(16) E. Perrotti, M. Lanzoni, G. Daniele, and M. De Malde, *Ann. Chim. (Rome)*, **55**, 485 (1965).

(17) G. Komppa and S. Beckmann, *Ann. Acad. Sci. Fenn., Ser. A*, **39** (7) (1934); *Chem. Abstr.*, **29**, 3668 (1935).

lowed by 1.2 g (10 mmol) of acetophenone and 330 mg (7 mmol) of $LiBH_3CN$. The resulting solution was stirred for 72 hr, then worked up as in procedure A to give 1.37 g (92%) of ~95% glpc pure amine. The product was added to a solution of saturated picric acid–ethanol and the solid product recrystallized from ethanol to give 2.38 g (75%) of *N*,*N*-dimethyl(α-phenethyl)amine picrate, mp 140–141° (lit.[18] mp 139–140°).

***N*-Methylpiperidine.** To a suspension of the bisulfite addition complex of glutaraldehyde (3.08 g, 10 mmol) in 50 ml of absolute methanol was added 1.3 g (20 mmol) of methylamine hydrochloride and 500 mg (9 mmol) of $NaBH_3CN$. The resulting mixture was stirred at 25° for 48 hr. The solution was then acidified to pH <2 with concentrated HCl and evaporated to dryness *in vacuo*. The residue was taken up in 10 ml of water, brought to pH >10 with 6 *N* KOH, saturated with NaCl, and extracted with eight 25-ml portions of ether. The combined extracts were dried ($MgSO_4$) and the ether was removed by distillation at atmospheric pressure. The residue was dissolved in 3 ml of ethanol and added to a solution of 2.3 g (10 mmol) of picric acid in 35 ml of ethanol. The solid was filtered and dried to give 1.38 g (43%) of *N*-methylpiperidine picrate, mp 147–149° (lit.[19] mp 148°).

***N*-Methyl(α-phenethyl)amine-d_1.** A solution of 240 mg (2 mmol) of acetophenone, 675 mg (10 mmol) of methylamine hydrochloride, and 125 mg (2 mmol) of $NaBD_3CN$ in 5 ml of absolute methanol was stirred for 72 hr at 25°. The methanol was removed *in vacuo*, and the residue was dissolved in 5 ml of 2 *N* HCl and extracted with two 5-ml portions of ether. The aqueous solution was brought to pH >10 with 6 *N* KOH, saturated with NaCl, and extracted with three 10-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 260 mg (97%) of glpc pure amine. Nmr and mass spectral analyses indicated >95% D_1. The product was isolated as its hydrochloride (245 mg, 72%), mp 177–180°.

***N*-Cyclopentylhydroxylamine.** A trace of bromocresol green was added to a solution of 350 mg (5 mmol) of hydroxylamine hydrochloride in 1 ml of water. Cyclopentanone (335 mg, 4 mmol) in 2 ml of methanol was added, and 6 *N* KOH was added dropwise until the color just changed from yellow to green. $NaBH_3CN$ (130 mg, 2 mmol) was added, and the solution was stirred 3 hr at 25°, HCl–methanol being added dropwise to just maintain the yellow color. The solution was poured into 5 ml of water and brought to pH >10 with 6 *N* KOH. After saturating with NaCl, the solution was extracted with four 5-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 357 mg of crude solid. One recrystallization from petroleum ether afforded 265 mg (66%) of *N*-cyclopentylhydroxylamine, mp 94–96° (lit.[16] mp 92–93°).

Synthesis of Amino Acids. The synthesis of phenylalanine is typical. A solution of 186 mg (1 mmol) of sodium phenylpyruvate, 500 mg (5 mmol) of ammonium bromide, and 100 mg (2 mmol) of $LiBH_3CN$ in 20 ml of methanol was stirred 48 hr at 25°. Concentrated HCl (5 ml) was added and, after stirring 1 hr at 25°, the solution was evaporated *in vacuo*. The residue was dissolved in 3 ml of water and added directly to a Dowex 50 (H^+ form) column containing ~100-mequiv capacity. The column was washed with 500 ml of distilled water, and the amino acid was then eluted with 300 ml of 1 *N* ammonium hydroxide. This fraction was evaporated *in vacuo* to give 81 mg (49%) of amorphous solid. Paper chromatographic analysis (Whatman No. 1, butanol–acetic acid–water 4:1:1) showed one ninhydrin spot with R_f identical with authentic phenylalanine.

Phenylalanine-2-*t* was prepared as above, except that only 200 mg of ammonium bromide, 58 mg of $NaBH_3CN$-*t*, and 10 ml of methanol were used. The product (77 mg, 47%) had a specific activity of $\sim 1 \times 10^5$ dpm/mg (16 μCi/mmol).

Tryptophan-^{15}N. To a solution of 205 mg (1 mmol) of 3-indolylpyruvic acid and 95 mg (1.2 mmol) of $^{15}NH_4NO_3$ (95% ^{15}N) in 15 ml of methanol was added 190 mg (3 mmol) of $NaBH_3CN$. The solution was adjusted to pH 7 (*i.e.*, 1 drop of solution caused no color change on wet blue or red litmus paper) and stirred at 25° for 36 hr. The reaction was worked up as for phenylalanine above to give 47 mg (23%) of tryptophan-^{15}N as an amorphous powder, with R_f on cellulose tlc identical with an authentic sample. Nitrogen isotope mass spectral analysis showed >47% ^{15}N (*i.e.*, >94% ^{15}N at C-2).

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