

## Sodium Cyanoborohydride – A Highly Selective Reducing Agent for Organic Functional Groups

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The utility of sodium cyanoborohydride as a selective reducing agent for organic synthesis is reviewed. Firstly a summary of the preparation and properties of sodium cyanoborohydride is given. Then some examples of sodium cyanoborohydride reductions of various systems are given including some applications of sodium cyanoborodeuteride.

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In einer Übersicht werden die Anwendungsmöglichkeiten des selektiv wirkenden Reduktionsmittels Natriumcyanoborhydrid bei organischen Synthesen aufgezeigt. Zunächst werden Herstellung und Eigenschaften des Reagenzes zusammengefaßt. Es folgt dann eine Reihe von Reduktionsbeispielen mit Natriumcyanoborhydrid an verschiedenen Systemen einschließlich einiger Anwendungen von Natriumcyanobordeuterid.

The synthetic organic chemist, being faced with the need to prepare compounds of ever-increasing complexity, has had the problems confronting him greatly simplified by the development of numerous selective reducing agents<sup>1</sup>. Reagents, that are capable of reducing a given functional group in the presence of various other sensitive functional groups, have been prepared by modifying the reducing power of complex metal hydrides. For example, substituted borohydrides are a particularly successful modification. The steric and electronic effects of the substituents greatly influence the reactivity of the borohydride ion<sup>2</sup>. Thus, sodium cyanoborohydride with its strongly electron-withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride.

The initial exploratory work on the utility of an alkali metal cyanoborohydride as a reducing agent resulted in almost totally negative results. Of all the functional groups studied only aldehydes were reported to be reduced<sup>3</sup>. Fortunately, the reagent was not forgotten and recent investigations have

shown that, under the proper conditions, sodium cyanoborohydride is an extremely useful reagent for the selective reduction of organic functional groups.

Within the last year the number of reported exploratory investigations of this reagent has decreased while the number of reported applications has increased substantially. Consequently, the time seems appropriate to review this interesting new reagent.

### 1. Preparation

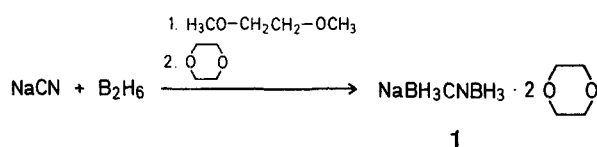
The first synthesis of a cyanoborohydride was reported by Wittig in 1951<sup>4</sup>. The lithium salt was prepared by reacting lithium borohydride with excess hydrogen cyanide under pressure. Subsequently, an improved synthesis was reported for the corresponding sodium salt<sup>5</sup>.

<sup>1</sup> For a recent excellent review of selective reductions, see H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, New York, 1972, chapters 12 and 13.

**Sodium Cyanoborohydride<sup>5</sup>:**

To a rapidly stirred slurry of sodium borohydride (80.2 g, 2.09 mol) in tetrahydrofuran (1000 ml) in a 2 l flask is added a solution of hydrogen cyanide in tetrahydrofuran (294 g containing 58.8 g of hydrogen cyanide) at 25°. Evolution of hydrogen occurs slowly during the addition. Following the addition, the reaction mixture is stirred for 1 h at 25° and then heated at reflux until hydrogen evolution has ceased. Filtration followed by vacuum removal of the tetrahydrofuran gives white solid sodium cyanoborohydride; yield: 120 g (91%).

The direct reaction of borane with sodium cyanide might appear to offer a more convenient method for preparing sodium cyanoborohydride. However, the reaction of diborane with sodium cyanide in 1,2-dimethoxyethane gave a diborane adduct that was precipitated and isolated as the etherate **1**<sup>6</sup>.



The infrared spectrum and <sup>11</sup>B-N.M.R. spectrum were only consistent with the structure [H<sub>3</sub>BCNBH<sub>3</sub>]<sup>⊖</sup>. A similar reaction of sodium cyanide with borane-tetrahydrofuran also resulted in the formation of NaBH<sub>3</sub>CNBH<sub>3</sub><sup>5</sup>.

**2. Purification**

The sodium cyanoborohydride prepared by the above procedure<sup>5</sup>, and the product available commercially is usually of sufficient purity for most applications. However, if ultra-pure material is required, then one of the following purification procedures should be used. The sodium cyanoborohydride is dissolved in tetrahydrofuran (20% w/v), filtered, and reprecipitated by a four-fold volume of dichloromethane<sup>5</sup>. The sodium cyanoborohydride is then collected and dried *in vacuo*. Alternatively, the compound is dissolved in dry nitromethane and filtered, and the filtrate is poured into a ten-fold volume of tetrachloromethane with vigorous stirring<sup>7</sup>. The white precipitate of sodium cyanoborohydride is filtered, washed several times with tetrachloromethane, and dried *in vacuo*. A third method for the purification of sodium cyanoborohydride is described below in detail and is necessary when the above procedures fail to improve the purity.

**Purification of Sodium Cyanoborohydride<sup>8</sup>:**

Sodium cyanoborohydride (10 g) is dissolved in tetrahydrofuran (80 ml) and 1 N methanolic hydrochloric acid is added until the pH reaches 9. The solution is then poured with stirring into dioxan (250 ml). The precipitate is collected and stirred for 2 h in ethyl acetate (250 ml). This solution is filtered, heated to reflux on a steam bath, and then dioxan (150 ml) is added slowly with swirling. This solution is slowly cooled to room temperature, chilled, and filtered. The crystalline dioxan complex is dried *in vacuo* for 4 h at room temperature, then for 4 h at 80°; yield: 6.74 g; purity > 98% sodium cyanoborohydride by iodometric titration<sup>9</sup>.

**3. Physical Properties**

Solvent-free sodium cyanoborohydride is a white amorphous powder, m. p. 240–242° (decomp.). Contact with air should be kept to a minimum because the compound is very hygroscopic.

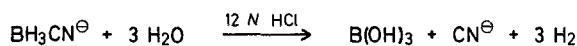
Sodium cyanoborohydride is highly soluble in a variety of solvents including water, alcohols, amines, and tetrahydrofuran but is insoluble in hydrocarbons. Complete solubility data are summarized in Table 1.

**Table 1.** Solubility of Sodium Cyanoborohydride in Various Solvents<sup>5</sup>

Solvent	Temperature	Solubility (g/100 g solvent)
THF	28°	37.2
	46°	41.0
	62°	42.2
water	29°	212
	52°	181
	88	121
methanol	24°	very soluble
ethanol	24°	slightly soluble
diglyme	25°	17.6
isopropylamine	25°	slightly soluble
diethyl ether	25°	insoluble
benzene	25°	insoluble
hexane	25°	insoluble

**4. Chemical Properties****4.1. Hydrolysis**

The utility of sodium cyanoborohydride as a reducing agent is greatly enhanced by its stability in acid to pH 3<sup>10</sup>. The hydrolysis of sodium cyanoborohydride is acid-catalyzed. However, its rate of hydrolysis is 10<sup>-8</sup> that of sodium borohydride<sup>11</sup>. The decomposition of sodium cyanoborohydride in water at pH 7 as measured by hydrogen evolution at concentrations from 10<sup>-3</sup> to 0.3 M is less than 0.5 mol % after 24 h<sup>7</sup>. In 12 N hydrochloric acid, relatively rapid hydrolysis does occur<sup>7</sup>.



The acid stability of sodium cyanoborohydride has resulted in numerous applications of this reagent that would not be possible with sodium borohydride (*vide infra*, Section 5). For example, sodium borohydride can be used to trap carbonium ions formed in the ionization of readily ionizable organic halides in an aqueous diglyme solution<sup>12</sup>. The rate of solvolysis would, of course, be enhanced in the presence of acid, but this would also rapidly destroy the sodium borohydride. This serious limitation is not present with sodium cyanoborohydride, which has been used to trap carbonium ions generated with hydrogen chloride in aqueous tetrahydrofuran<sup>13</sup>.

Measurement of the volume of hydrogen evolved upon hydrolysis in aqueous acid can be used for the quantitative analysis of sodium borohydride<sup>14</sup>. However, this procedure cannot be used conveniently to analyze sodium cyanoborohydride due to its slow rate of hydrolysis even in aqueous acid. Iodometric titration has been used to determine the purity of sodium borohydride<sup>9</sup> and sodium cyanoborohydride<sup>8,11</sup>. The half-reaction for this redox reaction is as shown<sup>7</sup>.



#### 4.2. Exchange

At pH 3, the hydrogen atoms of the cyanoborohydride anion can be readily exchanged for either deuterium or tritium<sup>10</sup>, thus permitting the direct synthesis of  $\text{NaBD}_3\text{CN}$  and  $\text{NaBH}_3\text{CN}-t$ <sup>8</sup>. When deuterium oxide is used, the rate of exchange is about 15 times faster than the rate of hydrolysis<sup>11</sup>. In the case of sodium borohydride, hydrolysis competes with exchange, thus exchange is barely detectable.

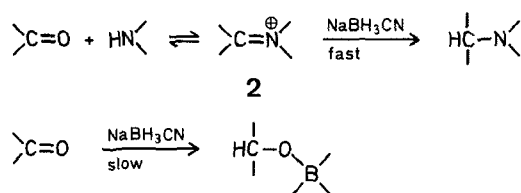
#### Sodium Cyanoborohydride-*t*<sup>8</sup>:

A trace of methyl orange is added to a solution of sodium cyanoborohydride (1.1 g) in water (10 ml) containing 100 mCi of tritium. The resulting solution is maintained at the red color (pH ~3) for 30 min by the dropwise addition of 0.2 M hydrochloric acid. Solid sodium carbonate is then added until pH 7, and the solution is evaporated to dryness *in vacuo*. The solid residue is stirred overnight with tetrahydrofuran (50 ml) then filtered. The resulting solution is evaporated *in vacuo* giving sodium cyanoborohydride-*t*; yield: 0.75 g; specific activity: 49.5  $\mu\text{Ci}/\text{mmol}$ .

### 5. Selective Reducing Properties

Sodium cyanoborohydride is a versatile reagent that will reduce a variety of organic functional groups with remarkable selectivity. For example, many selec-

tive reductions have resulted from the observation that an iminium ion (2) is reduced much faster than a carbonyl group<sup>8,10</sup>.

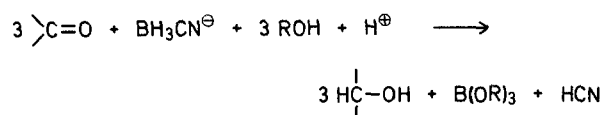


Also, the stability of sodium cyanoborohydride in protic solvents at low pH has allowed reductions to be carried out under conditions that would rapidly hydrolyze sodium borohydride. Finally, the solubility of sodium cyanoborohydride in polar aprotic solvents has further enhanced its utility as a reducing agent.


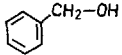


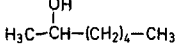
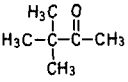
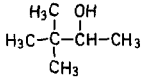
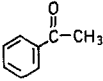
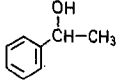


Sodium cyanoborohydride is a very selective reducing agent because, even under the diverse reaction conditions that have been employed, many sensitive functional groups have not been reduced. For example; amides, ethers, lactones, nitriles, nitro compounds and epoxides are inert toward this reagent.

#### 5.1. Reduction of Aldehydes and Ketones

Under neutral conditions in water or methanol there is negligible reduction of aldehydes and ketones. However, at pH 3–4, the rate of reduction is sufficiently rapid to be synthetically useful<sup>8,15</sup>. Since the reduction consumes acid, a buffered system is required or acid must be added to maintain the necessary low pH<sup>8</sup>.



**Table 2.** Reduction of Aldehydes and Ketones with Sodium Cyanoborohydride<sup>a</sup>

Compound	pH	Time	Product	Yield (%)
	4	2 h		87
	4	1 h		88
$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-(\text{CH}_2)_4-\text{CH}_3$	4	4 h		84
	3	2 h		86
	3	1 h		93
	4	1 h		67



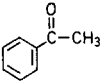
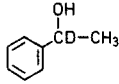
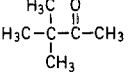
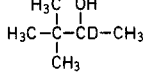
<sup>a</sup> Reductions in methanol at 25°, pH maintained by addition of methanolic hydrochloric acid. Results are taken from Lit.<sup>8</sup>.

The reductions are conveniently carried out in methanolic hydrogen chloride at 25°. Some specific examples are summarized in Table 2.

The reduction of cyclopentenone with sodium cyanoborohydride, under the conditions described in Table 2, gives mainly cyclopentanol<sup>8</sup>. However, this may not be a general result for  $\alpha,\beta$ -unsaturated systems. Recently, it was shown that, for the reduction of a series of conjugated ketones of the cholestenone type with sodium cyanoborohydride in tetrahydrofuran, the major product was usually the corresponding allylic alcohol<sup>16</sup>.

For sodium cyanoborodeuteride reductions, the recommended solvent is tetrahydrofuran/deuterium oxide and the pH is maintained by adding a solution of deuterium chloride/acetic acid-OD in tetrahydrofuran/deuterium oxide<sup>8</sup>. High yields of deuterated alcohols are possible as shown in Table 3.

**Table 3.** Reduction of Aldehydes and Ketones with Sodium Cyanoborodeuteride<sup>a</sup>

Compound	pH	Time	Product	Yield (%)
	4	4 h		85
	3	1 h		88
	3	2 h		84

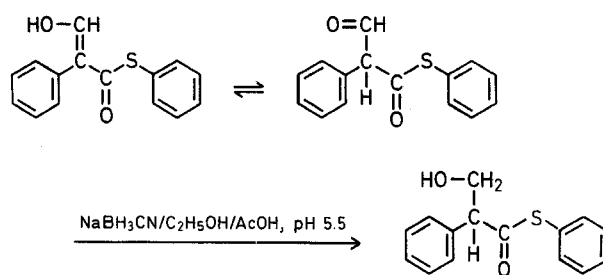
<sup>a</sup> Reductions carried out in tetrahydrofuran/deuterium oxide at 25°, pH maintained by addition of deuterium chloride/deuteroacetic acid in tetrahydrofuran/deuterium oxide. Results taken from Lit.<sup>8</sup>.

### 3,3-Dimethylbutan-2-ol-2-*d*<sup>8</sup>:

A trace of methyl orange is dissolved in deuterium oxide (0.1 ml) and added to tetrahydrofuran (2 ml). Pinacolone (300 mg, 3 mmol) and sodium cyanoborodeuteride (190 mg, 3 mmol) are added, and a solution of deuterium chloride/acetic acid-OD in tetrahydrofuran is added dropwise with stirring to maintain the red color. After 5 min, the red color persists. Stirring is then continued for 2 h. The solution is poured into water (100 ml), saturated with sodium chloride, and extracted with ether (3 × 10 ml). The combined extracts are dried (MgSO<sub>4</sub>) and evaporated *in vacuo* giving G.L.C. pure 3,3-dimethylbutan-2-ol-2-*d*; yield: 265 mg (84%). N.M.R. and mass spectral analysis show > 96% deuterium incorporation.

The mild conditions employed for these reductions with sodium cyanoborohydride should result in many applications for the selective reduction of aldehydes

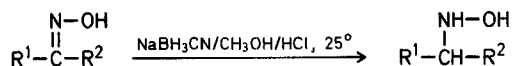
and ketones. Recently, a specific example was reported which showed that an aldehyde group can be selectively reduced with sodium cyanoborohydride in the presence of a thiol ester group<sup>17</sup>.



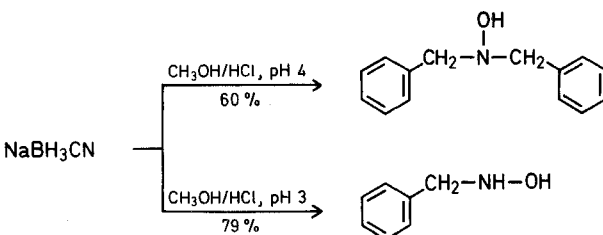
By changing the cation and solvent it is possible to carry out an even more selective reduction. Thus, tetrabutylammonium cyanoborohydride in acidified hexamethylphosphoric triamide selectively reduces aldehydes in the presence of almost all other functional groups including cyano, ester, amido, nitro, and even the keto group<sup>18</sup>.

## 5.2. Reduction of Oximes

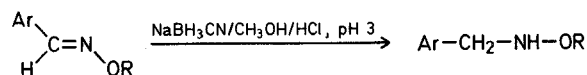
Under acid conditions, the reduction of ketoximes proceeds smoothly to the corresponding *N*-alkylhydroxylamine with no trace of the amine which would result from overreduction<sup>8</sup>.



The reduction of aldoximes is very pH dependent. When the reduction is carried out at pH 4, the major product is the dialkylhydroxylamine, while at pH 3, the major product is the monoalkylhydroxylamine<sup>8</sup>.



Reduction with sodium cyanoborohydride provides what is apparently the only known method for the conversion of *O*-alkylbenzaldoximes to the corresponding *N,O*-dialkylhydroxylamines<sup>19</sup>.



The reduction of oximes with borane/tetrahydrofuran provides an alternative method for the preparation of *N*-alkylhydroxylamines<sup>20</sup>. However, this procedure cannot be used to prepare *N,O*-dialkylhydroxylamines because reduction of oxime ethers<sup>21</sup> and oxime esters<sup>21,22</sup> with borane/tetrahydrofuran proceeds readily to give the corresponding amines in excellent yields. Also, catalytic hydrogenation of aryl ketoximes gives amines<sup>23</sup>, while aldoximes afford *N,N*-disubstituted hydroxylamines<sup>23</sup> and *O*-alkylbenzaldoximes give benzyl and dibenzylamine<sup>24</sup>.





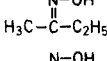
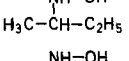
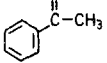
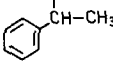
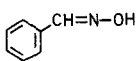
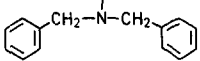
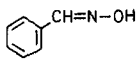
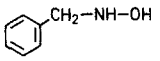
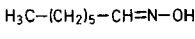
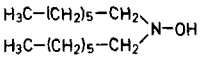
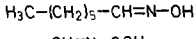
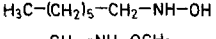
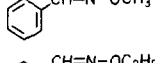
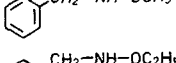
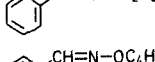
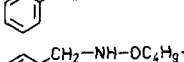
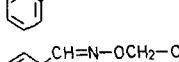
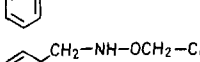
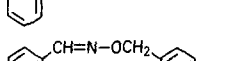
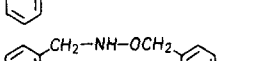
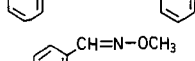
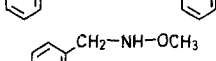


<sup>2</sup> The effect that alkyl and alkoxy substituents exert on the reactivity and selectivity of the borohydride ion was reviewed in a recent technical bulletin; "Trisubstituted Borohydride Reducing Agents", Aldrich Chemical Company, Inc., Milwaukee, Wisconsin, 53233, U.S.A.

<sup>3</sup> G. Drefahl, E. Keil, *J. Prakt. Chem.* **6**, 80 (1958).

The results obtained for the reduction of a variety of oximes with sodium cyanoborohydride are summarized in Table 4.

If the enamine is conjugated with a carbonyl group, the reduction becomes more difficult and acid must be added to maintain a pH of 4<sup>8</sup>.

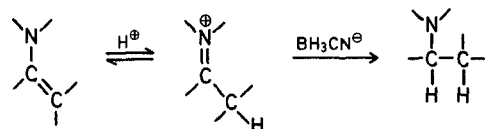
Table 4. Reduction of Oximes with Sodium Cyanoborohydride<sup>a</sup>

Oxime	pH	Product	Yield (%)	Reference
	4		66	8
	4		77	8
	4		73	8
	3		75	8
	4		60	8
	3		79	8
	4		57	8
	3		53	8
	3		58	19
	3		59	19
	3		67	19
	3		51	19
	3		56	19
	3		32	19

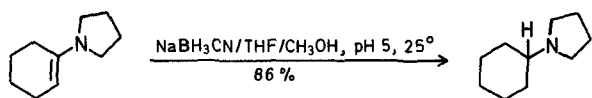
<sup>a</sup> Reductions carried out in methanol/hydrochloric acid at 25°

### 5.3. Reduction of Enamines

Although the enamine group itself should be resistant to reduction by sodium cyanoborohydride, rapid and reversible protonation of the  $\beta$ -carbon generates a readily reducible iminium salt.

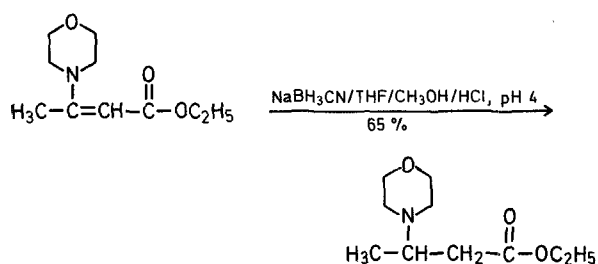


Simple enamines are rapidly reduced by sodium cyanoborohydride at an initial pH of 5 in a 15:1 tetrahydrofuran/methanol solvent mixture<sup>8</sup>.



<sup>4</sup> G. Wittig, *Liebigs Ann. Chem.* **573**, 209 (1951).

<sup>5</sup> R. C. Wade, E. A. Sullivan, J. R. Berschied, Jr., K. F. Purcell, *Inorg. Chem.* **9**, 2146 (1970).



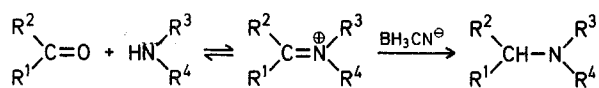
### 5.4. Reductive Amination of Aldehydes and Ketones

Since the iminium ion is reduced much faster than a carbonyl group, it is possible to reductively aminate an aldehyde or ketone by simply reacting the carbonyl compound with an amine at pH 6–8 in the presence of sodium cyanoborohydride.

<sup>6</sup> V. D. Aftandilian, H. C. Miller, E. L. Muetterties, *J. Amer. Chem. Soc.* **83**, 2471 (1961).

<sup>7</sup> J. R. Berschied, Jr., K. F. Purcell, *Inorg. Chem.* **9**, 624 (1970).

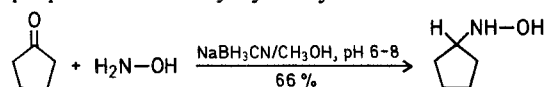
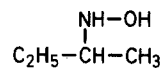
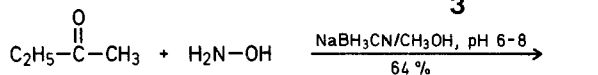
<sup>8</sup> R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Amer. Chem. Soc.* **93**, 2897 (1971).



The reaction is general for ammonia, primary and secondary amines, all aldehydes and unhindered ketones. Hindered and diaryl ketones fail to react and aromatic amines react somewhat sluggishly. The full scope of this reductive amination process is illustrated in Table 5.

The reductive amination process is not limited to the simple amines shown in Table 5. The reaction

of a ketone with hydroxylamine has been used to prepare the *N*-alkylhydroxylamines **3** and **4**<sup>8</sup>.

**3****4**

**Table 5.** Reductive Aminations with Sodium Cyanoborohydride<sup>a</sup>






















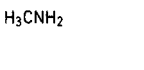
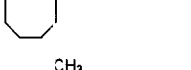







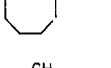

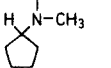
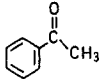
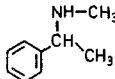
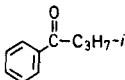
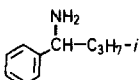
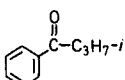
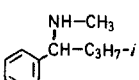
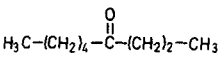

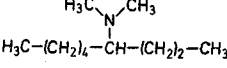
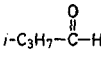

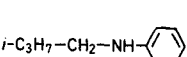

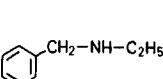
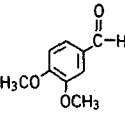
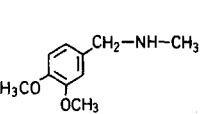
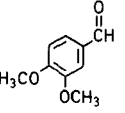

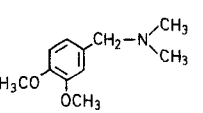
Compound	Amine	Product	Yield (%) <sup>b</sup>
	NH <sub>3</sub>		45
	H <sub>3</sub> CNH <sub>2</sub>		41
			43 <sup>c</sup> , 71 <sup>d</sup>
			79
	H <sub>3</sub> CNH <sub>2</sub>		61
			63
	H <sub>3</sub> CNH <sub>2</sub>		56
			59
			79
			57
	NH <sub>3</sub>		48
			47 <sup>e</sup>
	NH <sub>3</sub>		77

Table 5. continued.

Compound	Amine	Product	Yield (%) <sup>b</sup>
	H <sub>3</sub> CNH <sub>2</sub>		78
	NH <sub>3</sub>		59
	H <sub>3</sub> CNH <sub>2</sub>		90 <sup>f</sup>
			77
			78
	C <sub>2</sub> H <sub>5</sub> -NH <sub>2</sub>		80
	H <sub>3</sub> CNH <sub>2</sub>		51
			59

<sup>a</sup> Reductions in absolute methanol at 25°, pH 6-8. Results taken from reference 8.

<sup>b</sup> Isolated yield of recrystallized solid derivative.

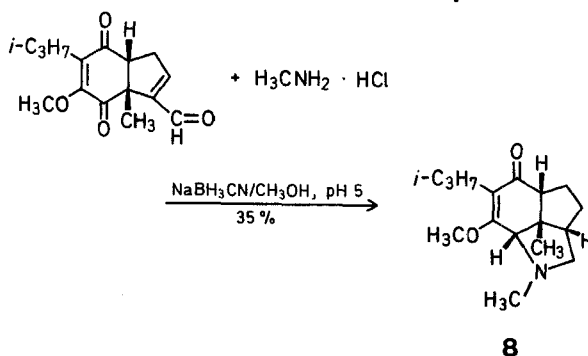
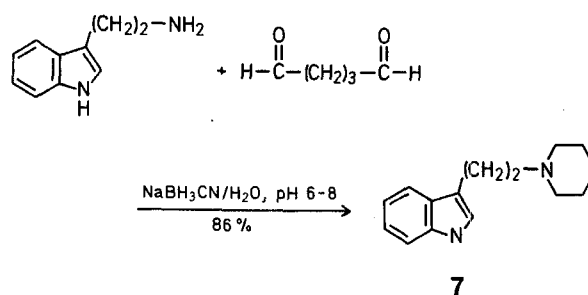
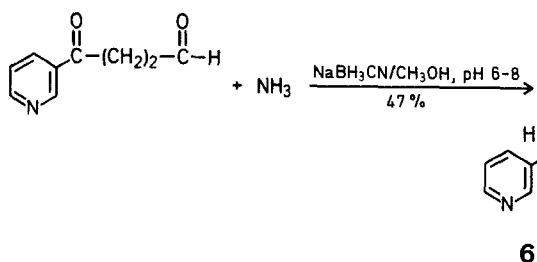
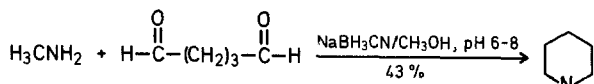
<sup>c</sup> Somewhat improved yield was later reported<sup>25</sup>.

<sup>d</sup> The use of 3A molecular sieves to absorb the water generated in the reaction resulted in the improved yield.

<sup>e</sup> Reaction carried out in the presence of 3A molecular sieves.

<sup>f</sup> When dimethylamine was used, the amine product was formed in only 5% yield.

The reaction of a dicarbonyl compound with an amine in the presence of sodium cyanoborohydride provides an interesting new synthesis of nitrogen-heterocycles, as illustrated by the preparation of **5**<sup>8</sup>, **6**<sup>8</sup>, **7**<sup>26</sup>, and **8**<sup>27</sup>.



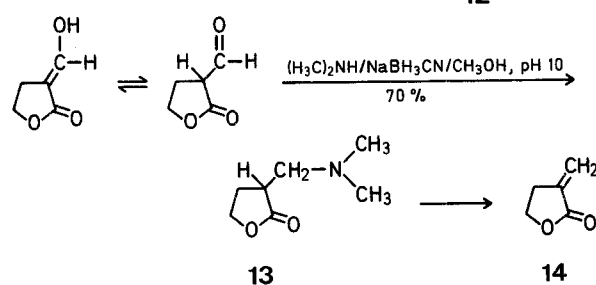
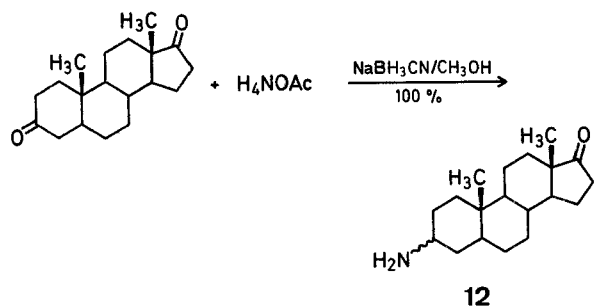
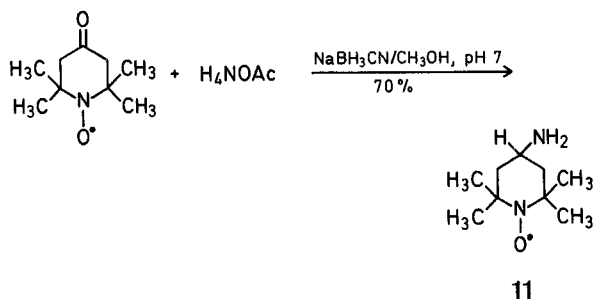
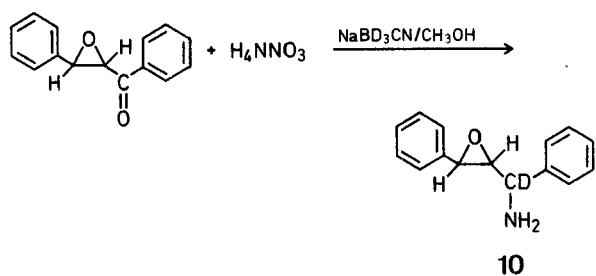
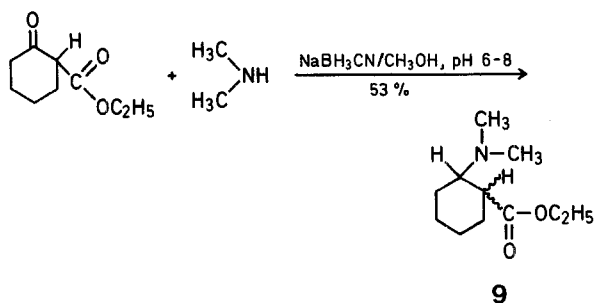
<sup>9</sup> D. A. Lyttle, E. H. Jensen, W. A. Struck, *Anal. Chem.* **24**, 1843 (1952).

<sup>10</sup> R. F. Borch, H. D. Durst, *J. Amer. Chem. Soc.* **91**, 3996 (1969).

<sup>11</sup> M. M. Kreevoy, J. E. C. Hutchins, *J. Amer. Chem. Soc.* **91**, 4329 (1969).

The mild conditions that are employed for these reductive aminations obviously indicate that numerous highly selective reductions should be pos-

sible. Recently, it has been shown that reductive amination with sodium cyanoborohydride can be used to prepare each of the following functionally substituted amines; aminoester (**9**)<sup>8</sup>, aminoepoxide (**10**)<sup>28</sup> and aminonitroxide free radical (**11**)<sup>29</sup>. An unhindered ketone can be selectively aminated in the presence of a relatively hindered ketone to give the aminoketone **12**<sup>30</sup>. Finally, a selective amination of a formyllactone gave the aminolactone **13**<sup>31</sup>. This was then used as the key step in a convenient and high yield synthesis of the plant antifungal agent, tulipalin A (**14**)<sup>32</sup>.



The reductive amination of substituted pyruvic acids, as summarized in Table 6, provides a useful new synthesis of *dl*- $\alpha$ -amino acids<sup>8</sup>. This procedure is apparently the most efficient and economical route available for preparing <sup>15</sup>N-labeled amino acids.

**Table 6.** Reductive Amination of Pyruvic Acids with Sodium Cyanoborohydride<sup>a</sup>

Keto Acid	Amino Acid	Yield (%) <sup>b</sup>
		52
		50
		51
		49
		46
		37
		23 <sup>c</sup>

<sup>a</sup> Reductions in methanol at 25°, pH 6-8 using NH<sub>4</sub>Br. Results taken from reference 8.

<sup>b</sup> Isolated yield of purified amino acid.

<sup>c</sup> Reduction using <sup>15</sup>NH<sub>4</sub>NO<sub>3</sub>.

### 5.5. Reductive Alkylation of Amines and Hydrazines

A mild and efficient method for the synthesis of tertiary methylated amines has been developed that involves simply the reductive amination of formaldehyde<sup>33</sup>. The reaction of an aliphatic or aromatic amine with aqueous formaldehyde and sodium cyanoborohydride in acetonitrile results in excellent isolated yields of methylated amines, as shown in Table 7.

<sup>12</sup> H. C. Brown, H. M. Bell, *J. Org. Chem.* **27**, 1928 (1962).

<sup>13</sup> M. M. Kreevoy, D. C. Johnson, *Croat. Chem. Acta* **45**, 511 (1973); *C.A.* **80**, 26843d (1974).

<sup>14</sup> This technique is discussed in the technical bulletin: "Quantitative Analysis of Active Boron Hydrides", Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233, U.S.A.

<sup>15</sup> M. M. Kreevoy, R. F. Borch, J. E. C. Hutchins, *U.S. Patent* 3,647,890 (1972); *C.A.* **76**, 112222 (1972).

<sup>16</sup> M.-H. Boutigue, R. Jacquesy, Y. Petit, *Bull. Soc. Chim. France* **1973**, 3062.

<sup>17</sup> J. Domagala, J. Wemple, *Tetrahedron Lett.* **1973**, 1179.

<sup>18</sup> R. O. Hutchins, D. Kandasamy, *J. Amer. Chem. Soc.* **95**, 6131 (1973).

<sup>19</sup> C. Bernhart, C.-G. Wermuth, *Tetrahedron Lett.* **1974**, 2493.

<sup>20</sup> H. Feuer, B. F. Vincent, Jr., R. S. Bartlett, *J. Org. Chem.* **30**, 2877 (1965).



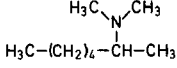

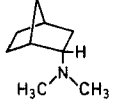
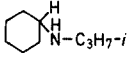
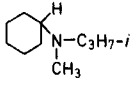
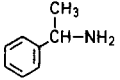
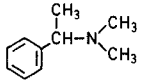
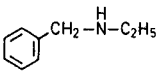
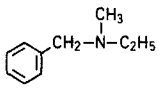

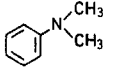
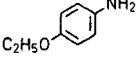
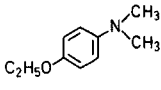
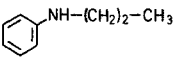
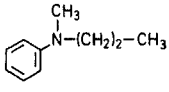

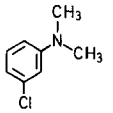
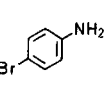
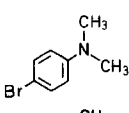

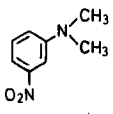
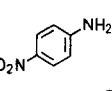
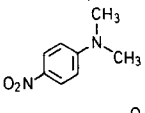
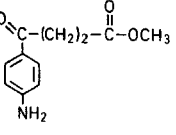
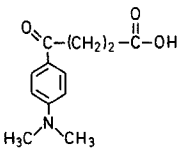
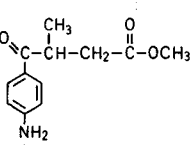
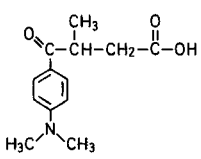
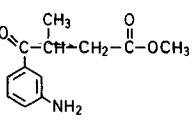
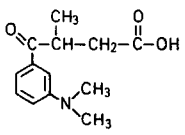
<sup>21</sup> H. Feuer, D. M. Braunstein, *J. Org. Chem.* **34**, 1817 (1969).

<sup>22</sup> A. Hassner, P. Catsoulacos, *Chem. Commun.* **1967**, 590.

<sup>23</sup> G. Vavon, M. Krajinovic, *Bull. Soc. Chim. France* **1928**, 231; and references cited therein.



**Table 7.** Reductive Methylation of Amines with Sodium Cyanoborohydride<sup>a</sup>

Compound	Product	Yield (%) <sup>b</sup>	Reference
		84	33
$\text{H}_3\text{C}-(\text{CH}_2)_4-\text{CH}-\text{NH}_2$		82	33
		75	33
		87	33
		81	33
		85	33
		92	33
		85	33
		83	33
		86	33
		87	33
		46 <sup>c</sup>	33
		68	33
		100	34
		59	34
		96	34

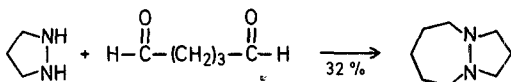
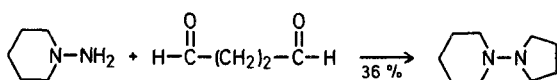
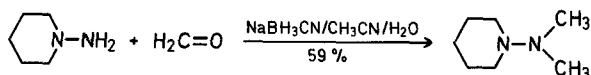
<sup>a</sup> Reduction in acetonitrile/acetic acid at 25°, pH 7, using an excess of 37% aqueous formaldehyde.<sup>b</sup> Isolated yields.<sup>c</sup> Monomethylated product also formed (18%).

The mild conditions, ease of experimental manipulation and the high yield of pure product appear to make this the method of choice for the reductive methylation of amines.

### 3-(*p*-Dimethylaminobenzoyl)propanoic Acid<sup>34</sup>:

A solution of methyl 3-(*p*-aminobenzoyl)propanoate (1.49 g, 7.20 mmol) and formaldehyde (6.2 ml of 37% aqueous solution) in acetonitrile (30 ml) is added to sodium cyanoborohydride (1.37 g, 23.2 mmol). Acetic acid (0.77 ml) is added to the stirred mixture and stirring is continued for 2 h. Additional acetic acid (0.77 ml) is added and stirring is continued for an additional 0.5 h. The solution is then diluted with ether (100 ml) and washed with 1 *N* sodium hydroxide solution. The organic layer is dried, evaporated, heated at reflux for 1.5 h with 6 *N* HCl solution (20 ml), filtered while hot, evaporated, and triturated with acetone (25 ml) to give 3-(*p*-dimethylaminobenzoyl)propanoic acid; yield: 1.62 g (100%); m. p. 172–175°.

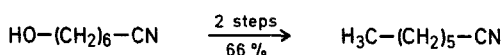
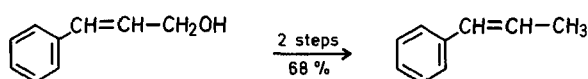
Hydrazines can also be reductively alkylated using sodium cyanoborohydride to provide a simple synthesis of some interesting tetraalkylhydrazines<sup>35</sup>.



### 5.6. Reductive Displacement of Halides and Tosylates

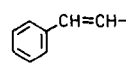
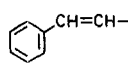
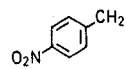
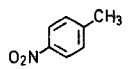
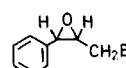
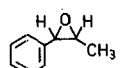
Sodium cyanoborohydride in hexamethylphosphoric triamide provides a rapid, convenient and exceedingly selective system for the reductive removal of iodo, bromo and tosyloxy groups<sup>36</sup>. The results summarized in Table 8 give an indication of the scope of this reductive displacement procedure.

Primary alcohols may be converted by a simple two-step-in-one process to the corresponding hydrocarbons. The process involves conversion of the alcohol to the iodide with methyltriphenoxyphosphonium iodide in hexamethylphosphoric triamide at room temperature followed by addition of sodium cyanoborohydride and stirring at 70°<sup>36</sup>. Two examples are given below.



The superior selectivity possible for this reductive displacement reaction is demonstrated by the inertness toward almost all other functional groups including ester, amide, nitro, chloro, cyano, alkene and even such sensitive groups as epoxide, ketone and aldehyde<sup>36</sup>. This selectivity becomes even more pronounced when tetrabutylammonium cyanoborohydride is used<sup>18</sup>.

Table 8. Reductive Displacements with Sodium Cyanoborohydride<sup>a</sup>

Compound	Temperature	Time	Product	Yield (%) <sup>b</sup>
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>11</sub> -J	25°	3.5 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	91 <sup>c</sup>
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>11</sub> -Br	70°	1.1 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	97
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>11</sub> -Cl	100°	27 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	72
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>11</sub> -OTos	70°	6.5 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	78 <sup>d</sup>
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>5</sub> - $\overset{\text{J}}{\text{C}}\text{H}-\text{CH}_3$	70°	2 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>6</sub> -CH <sub>3</sub>	91
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>9</sub> - $\overset{\text{Br}}{\text{C}}\text{H}-\text{CH}_3$	70°	24 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	97
H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>3</sub> - $\overset{\text{Br}}{\text{C}}\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OC}_2\text{H}_5$	70°	3 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>4</sub> - $\overset{\text{O}}{\parallel}{\text{C}}-\text{OC}_2\text{H}_5$	90
	70°	0.5 h		76
	70°	1.5 h		85 <sup>c</sup>
	70°	12 h		63
Br-(CH <sub>2</sub> ) <sub>6</sub> -CN	100°	3 h	H <sub>3</sub> C-(CH <sub>2</sub> ) <sub>5</sub> -CN	85

<sup>a</sup> Reductions in hexamethylphosphoric triamide. Results taken from reference 36.

<sup>b</sup> Yield by G.L.C. unless indicated otherwise.

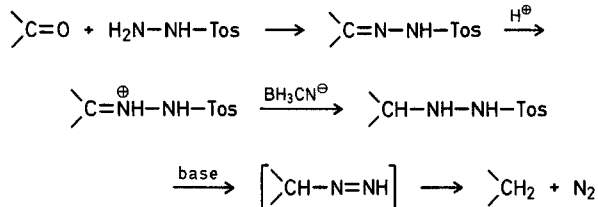
<sup>c</sup> Isolated yield of 88–90% for reduction of 1-iododecane<sup>37</sup>.

<sup>d</sup> Isolated yield of 73–78%<sup>37</sup>.

<sup>e</sup> Isolated yield of purified product.

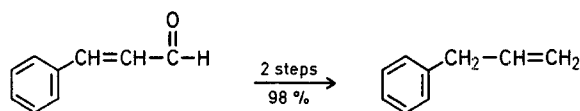
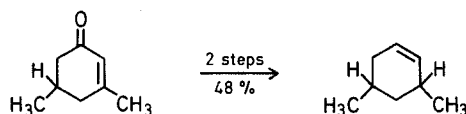
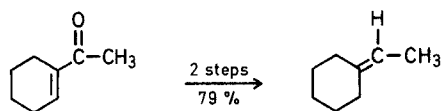
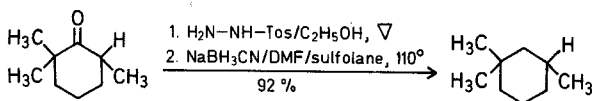
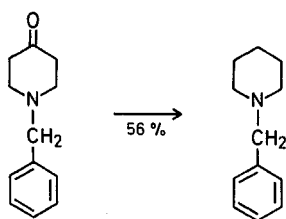
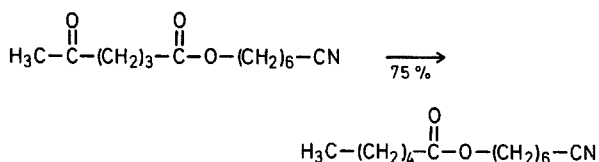
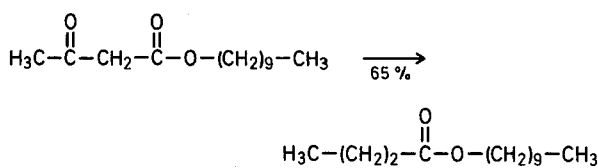
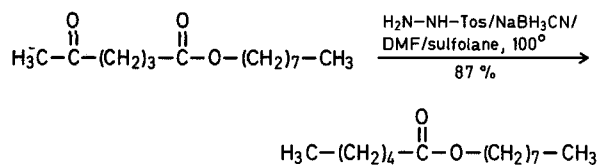
## 5.7. Deoxygenation of Aldehydes and Ketones

The propensity for sodium cyanoborohydride to reduce iminium ions has resulted in the development of still another useful synthetic reaction. The reduction of aliphatic ketone and aldehyde tosylhydrazones with sodium cyanoborohydride in acidic 1:1 dimethylformamide/sulfolane provides a mild, selective, convenient and high-yield alternative to Wolff-Kishner and Clemmensen reductions<sup>38,39,40</sup>.



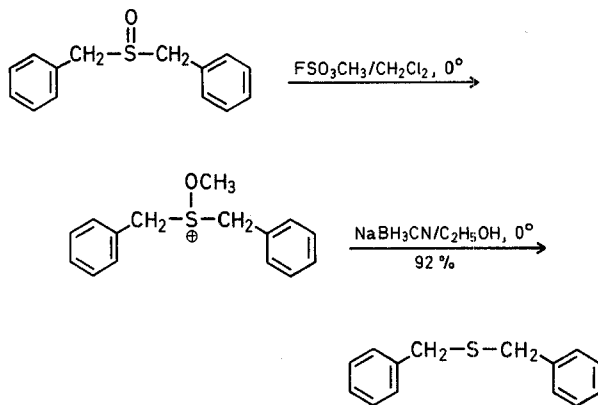
The prior preparation of the tosylhydrazone is unnecessary in many cases since the slow rate of carbonyl reduction permits the *in situ* generation from tosylhydrazine and carbonyl compound.

A number of general deoxygenation procedures have been developed depending on the structure of the carbonyl compound. The original investigation, in which over 60 different carbonyl compounds were studied, should be consulted for experimental details<sup>39</sup>, but the following examples should indicate the utility and selectivity of this useful method for the deoxygenation of carbonyl compounds.



Aryl carbonyl compounds proved to be quite resistant to reduction by this method regardless of the procedure used<sup>39</sup>. However, this might prove to be useful because aliphatic ketones and aldehydes could probably be selectively removed in the presence of an aryl carbonyl group.

A procedure has also been developed for the deoxygenation of sulfoxides using sodium cyanoborohydride which involves the prior formation of an alkoxysulfonium salt using methyl fluorosulfonate<sup>41</sup>.



In conclusion, the stability and reactivity of the cyanoborohydride ion in aqueous systems at pH 6–8 indicate the potential for carrying out imine reductions and carbonyl aminations on complex biological systems. Recently, such an application has been reported where the imino linkage between 11-

<sup>24</sup> L. W. Jones, R. T. Major, *J. Amer. Chem. Soc.* **52**, 669 (1930).

<sup>25</sup> R. F. Borch, *Org. Syn.* **52**, 124 (1972).

<sup>26</sup> G. W. Gribble, *J. Org. Chem.* **37**, 1833 (1972).

<sup>27</sup> A. S. Kende, T. J. Bentley, R. A. Mader, D. Ridge, *J. Amer. Chem. Soc.* **96**, 4332 (1974).

<sup>28</sup> A. Padwa, P. Cimiluca, D. Eastman, *J. Org. Chem.* **37**, 805 (1972).

<sup>29</sup> G. M. Rosen, *J. Med. Chem.* **17**, 358 (1974).

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