

SYNTHETIC REDUCTIONS IN CLANDESTINE AMPHETAMINE AND METHAMPHETAMINE LABORATORIES: A REVIEW

ANDREW ALLEN^a and THOMAS S. CANTRELL^b

^a*Ashtabula County Laboratory, 345 Rogers Place, Ashtabula, OH 44004 and* ^b*Chemistry Department, American University, Washington, DC 20016 (U.S.A.)*

(Received June 8th, 1988)

(Revision received November 29th, 1988)

(Accepted December 5th, 1988)

Summary

A review of synthetic reductions utilized in the clandestine manufacture of amphetamine and methamphetamine is presented. General discussions on the mechanism of heterogeneous catalysis, dissolving metals, hydrides and non-metal reductions used in the manufacture of amphetamine and methamphetamine with over 80 references are presented.

Key words: Amphetamine; Methamphetamine; Synthesis; Clandestine laboratories

Introduction

This review addresses reductions in clandestine methamphetamine and amphetamine synthesis. Central to the diverse routes published for the synthesis of methamphetamine and amphetamine is a reductive step at some point in the synthesis. Of 95 references surveyed concerning the synthesis of these controlled drugs, all but ten utilize a reductive approach. Since such diversity exists in these approaches, we felt that a composite literature review and discussion of the chemistry involved would help forensic chemists charged with investigating these clandestine laboratories. Secondly, we felt that a composite reference list would be of assistance in correlating notes or procedures found in clandestine laboratory sites to the open literature. Finally, only two open literature review articles in this forensic area have appeared and both were devoid of extensive references [1,2].

An overview of synthetic approaches to methamphetamine and amphetamine utilizing reductive routes is outlined in Tables 1 and 2. Table 1 is organized by the type of catalytic surface or reductive species; i.e. Pd, Pt, LiAlH₄, HCOOH, etc. Table 2 is organized by the synthetic route or intermediate; i.e. Leuckart, Schiff base, oxime, nitrostyrene, etc. Figures 1–12 illustrate the chemical formulas of the chemical reduction routes to amphetamine and methamphetamine. References [3,72] are annotated with the type of reductive catalyst/reagent and route utilized. Chemical Abstract citations

TABLE 1
METHAMPHETAMINE OR AMPHETAMINE

	<i>Refs.</i>
<i>Heterogeneous reductions</i>	
<i>(external source of hydrogen)</i>	
A. Pd	3-17,39
B. Pd/C	7,9,12,15-17
C. Pd/BaSO ₄	5,8
D. Pt	18-24
E. Pt/C	23
F. CuO, CaSO ₄ , BaSO ₄	25
G. Raney Nickel (Ni-Al)	26-38
<i>Heterogeneous reductions</i>	
<i>(internal source of hydrogen)</i>	
H. CaH ₂ /Pd, HCl	39
<i>Dissolving metal reductions</i>	
<i>('Internal' electrolytic)</i>	
I. Al-Hg	40-45
J. Al-Pd, HCl	54
K. Na alcohol	46-49
L. Na-Hg	50,51
M. Fe, HCl	52,53
N. Zn, HCl	54
O. Zn-Cu, HCl	54
P. Zn-Pd, HCl	54
Q. Zn-Cu-Pd, HCl	54
<i>Metal hydride reductions</i>	
<i>(source of hydride)</i>	
R. NaBH ₄	55,56
S. NaCNBH ₃	57
T. LiAlH ₄	58-62
<i>Non-metal reductions</i>	
U. HI	63; pers. comm.*
V. HCOOH	64-72

*J. Heagy, personal communication, from information gathered by attending clandestine laboratory sites. Drug Enforcement Administration, 450 Golden Gate Avenue, San Francisco, CA 94102.

[C.A. Vol.: page (year)] are included for each reference for ease of cross reference with cryptic notes often found in clandestine laboratory sites. Finally, the recurrent use of the terminology "open literature" refers to legitimate, accredited journals as opposed to underground publications or notes passed between clandestine manufacturers.

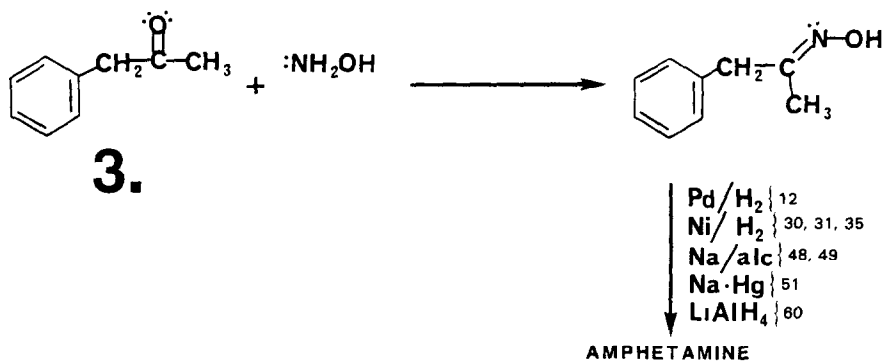
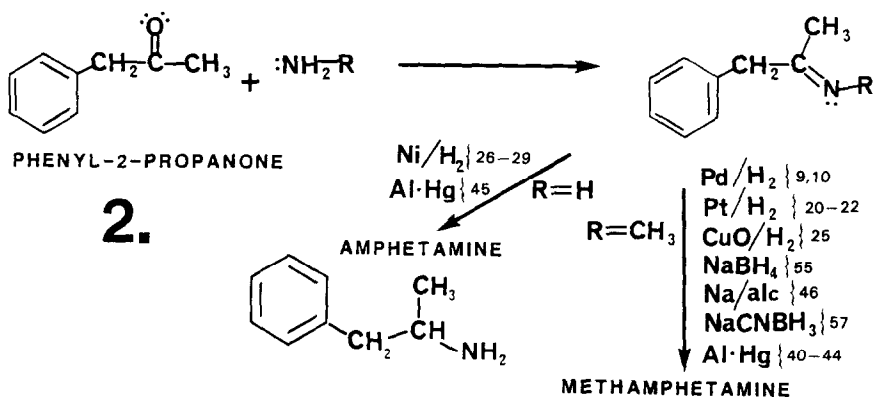
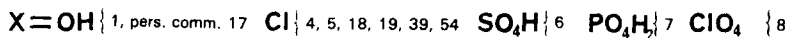
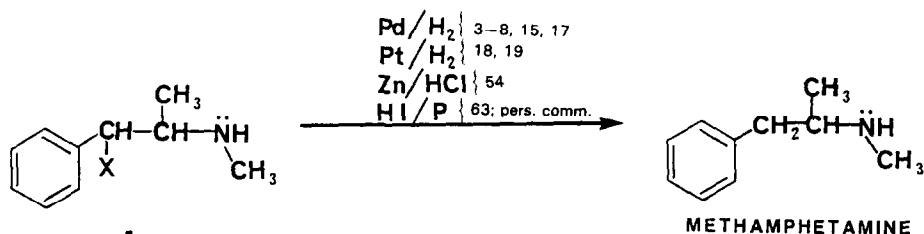
TABLE 2
METHAMPHETAMINE AND AMPHETAMINE VIA REDUCTION

	<i>Route no.</i>
<i>Methamphetamine via</i>	
Ephedrine	1
(A) Direct [3,8,17; J. Heagy ^a]	
(B) Halo analog [3-5,17,18,19,39,54]	
(C) Sulfate ester [6]	
(D) Phosphate ester [7]	
(E) Perchlorate ester [8]	
Schiff's base [10,20,21,22,25,40-44,46,55,57]	2
Thiazole [47]	9
Leuckart [58,64,66]	8
<i>d</i> -Phenylalanine carbamate [59]	10
<i>N</i> -Formyl [58,66]	8
<i>Amphetamine</i>	
Oxime [11,12,30,31,48,49,60]	3
Nitrostyrene [13,32,33,35,50,61]	4
2-Keto oxime [14-16,36,38,51]	5
Hydrazone [23,34]	6
Schiff's base [26-29,45]	2
3-Iodo analog [62]	11
Leuckart [65,67-70]	8
Demercuration [56]	12

^aSee footnote Table 1.

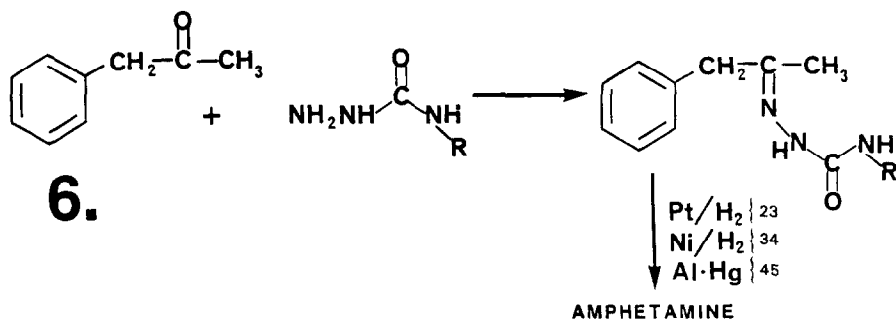
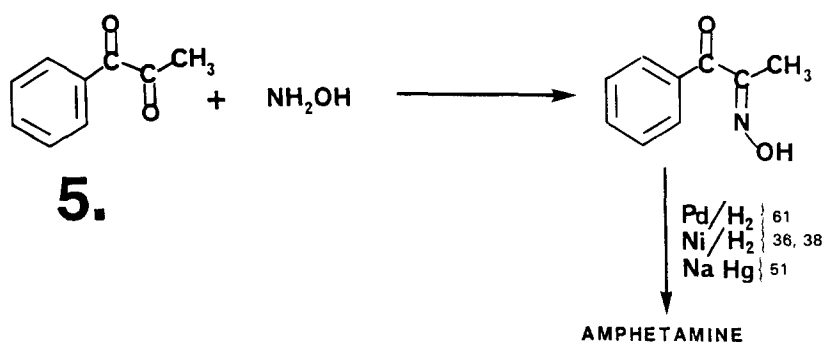
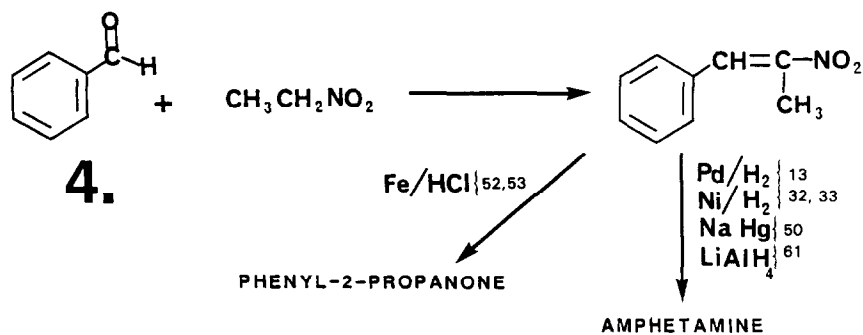
Heterogeneous catalysis

The role of heterogeneous catalytic hydrogenation and hydrogenolysis in organic synthesis is replete in the literature. However, the mechanism of the catalyst's role has remained elusive due mainly to the difficulty of studying such heterogenous systems. Recent research in this area has shown that a system charged with H₂ and D₂ in the presence of a catalyst yields HD. This has been interpreted as the catalyst's coordination with molecular H₂ and weakening or disruption of the H-H bond [87,88]. Studies by Maier et al. (pers. commun., Dept. of Chemistry, Univ. of California, Berkeley, CA 94720), in which the catalytic surface has been coated with SiO₂, have revealed that the H-H (which penetrates the SiO₂ layer to coordinate with the catalytic surface) is truly ruptured, yielding ^oH. Furthermore, hydrogenation of an organic species (incapable of penetrating the SiO₂ layer) occurred. This suggests that coordination between the organic moiety and the catalytic surface may not be necessary. "Selectivity" for an organic substrate in some catalytic metal hydrogenation systems has recently been shown to be dependent upon the topology of the catalytic surface [89]. Further work in this area will be followed with interest.



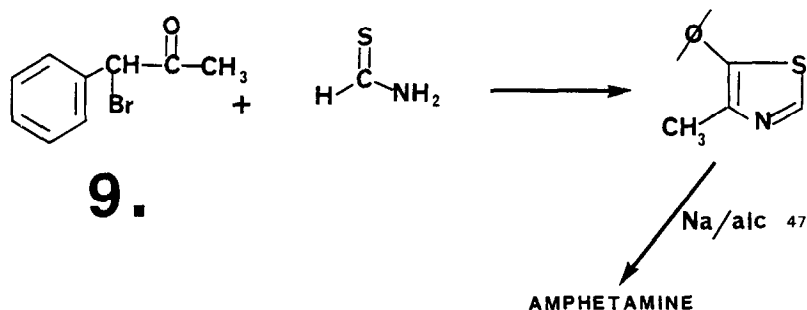
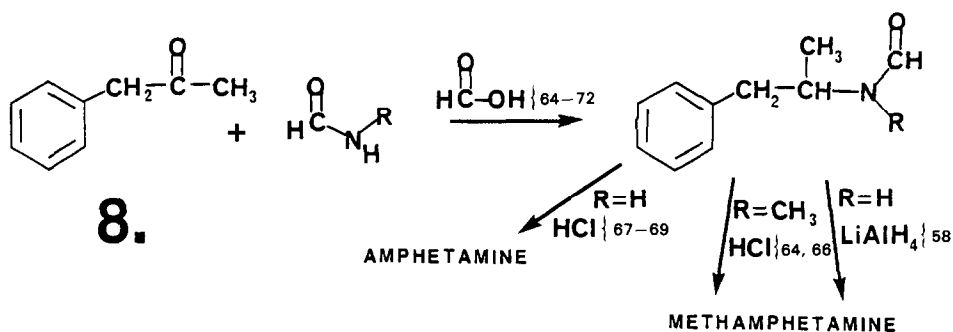
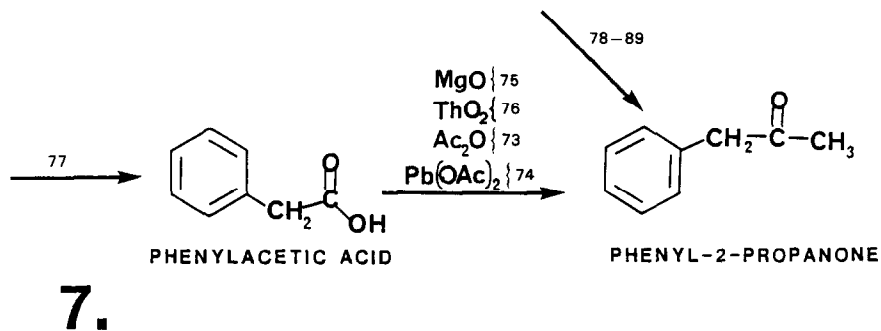
Figs. 1-3.

Heterogeneous catalytic reduction of ephedrine to methamphetamine in clandestine laboratories is most often achieved with palladium [3-8, 15, 17, 39]; the use of platinum (Adams Catalysis) is second in frequency [18, 19] (Fig. 1). Similar correlations apply to the reduction of phenylpropanolamine to amphetamine utilizing palladium, platinum and Raney Nickel.



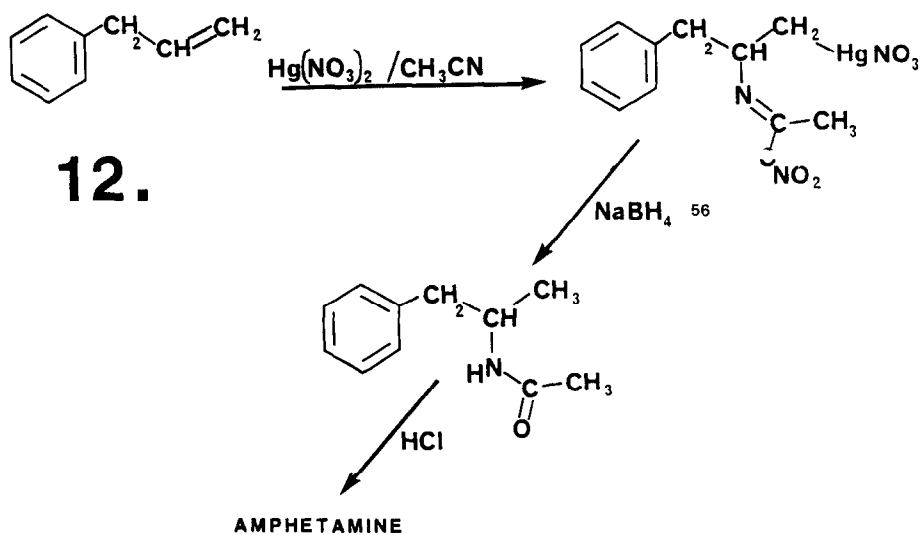
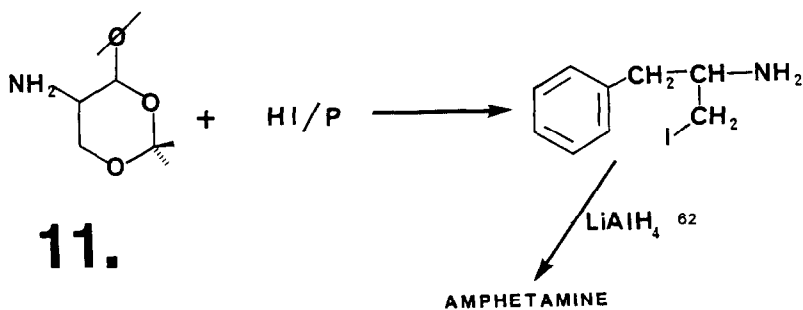
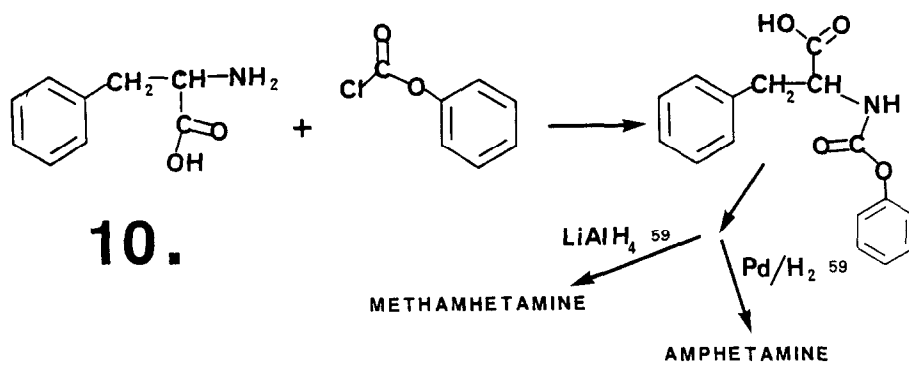
Figs. 4–6.

Hydrogenolysis of ephedrine or phenylpropanolamine (here hydrogenolysis is defined as reduction of C-X) is not a result of reduction of the benzylic carbon-OH bond. The actual moiety reduced is C-X, where X refers to halogen [3–5, 17–19, 39,54] sulfate [6], phosphate [7] or perchlorate [8] esters (Fig. 1). This moiety (C-X) may be produced in situ [3,17] or synthesized externally, isolated and then reduced [4,9,18,19,39,54]. The stereochemistry and analytical methodology for methamphetamine prepared from ephedrine and pseudoephedrine has recently been addressed [92,93].



Figs. 7-9.

Heterogeneous catalysis has been used to reduce the imine bond of Schiff bases formed with phenyl-2-propanone and ammonia or methylamine in order to produce amphetamine [26-29] or methamphetamine [9,10,20-22,25] (Fig. 2). When heterogeneous catalysis is utilized in this Schiff's base reduction, a competing reaction, that of P-2-P reduction to 1-phenyl-2-propanol, limits the yield of amphetamine or methamphetamine. Additions of large excesses of the amine component in these reactions have been employed to suppress the



Figs. 10–12.

ketone reduction. This has limited applicability, since the optimum pH for the Schiff's base production is between pH 6 and 7.

Other clandestine routes, although less popular, which have open literature references utilizing heterogenous catalysis for the synthesis of amphetamine are oxime reduction [12,30,31,35] (Fig. 3), nitrostyrene reduction [13,32,33] (Fig. 4), 2-keto-oxime reduction [16,36,38] (Fig. 5) and hydrazone reduction [23,34] (Fig. 6).

Precursors to amphetamine (phenylpropanolamine) and methamphetamine (ephedrine) have been synthesized with the aid of heterogeneous catalysis [16,38], (Fig. 5).

Dissolving metal reductions

Dissolving metal reductions, in particular aluminum, continue to be the most popular synthetic routes to methamphetamine and amphetamine in clandestine laboratories in the United States. Although molecular H_2 is produced as the metal dissolves, this is generally considered a detriment to the reduction of the organic species. The actual reductive mechanism does not involve molecular H_2 but is, in fact, a result of an "internal electrolytic process". Electron transfer from the metal to a heteroatom results in a radical carbon which abstracts hydrogen from solution to complete reduction. In metals where higher oxidation states are present (i.e. Al, Mg, Zn) dimers may form as a result of intramolecular radical combination [54,90,91].

Poisoning of catalysis is one approach used to minimize rapid dissolution of the metal and to abate evolution of H_2 . Amalgams made between sodium and mercury have the effect of diminishing the activity of the parent metal thus slowing dissolution of the reducing species. Amalgamation between aluminum and mercury has the added benefit of preventing oxide formation on the surface of aluminum in contact with air. Aluminium-mercury amalgam serves to poison the metal somewhere between the extremes of the over-active metal and the inactive metal oxide.

In the clandestine manufacture of amphetamine and methamphetamine the most popular route is via aluminum-mercury amalgam reduction of the Schiff base adduct of phenyl-2-propanone (P-2-P) and the appropriate amine [40-45] (Fig. 2). This popularity persists despite U.S. Government control (Schedule II) of P-2-P in 1980. This controlled status has resulted in an upsurge in the clandestine manufacture of P-2-P. A variety of synthetic routes have surfaced in clandestine laboratories, primarily through phenylacetic acid [73-77] (Fig. 7). Alternatives to the phenylacetic acid (now on a reporting schedule in some states) synthesis of P-2-P have appeared [78-89]. One approach to P-2-P utilizes a dissolving metal reduction of nitrostyrene with iron and hydrochloric acid [52,53] (Fig. 4).

Clandestine laboratories which utilize other dissolving metal reduction routes have been infrequently encountered. However, reduction of a Schiff base to methamphetamine [46] (Fig. 2) and of 5-phenyl-4-methylthiazole to

amphetamine [47] (Fig. 9) using sodium in alcohol are cited in the open literature. Additionally, Na/alcohol reduction of an oxime [48,49] (Fig. 3), Na/Hg amalgam reduction of a nitrostryene [50] (Fig. 4) or a 2-keto-oxime [51] (Fig. 5) to amphetamine and zinc/HCl reduction of chloro analogs of ephedrine to methamphetamine [54] (Fig. 1) are also cited in the literature.

Metal hydride reduction

Metal hydride reductions have not captured the imagination of clandestine laboratory chemists like the remainder of the scientific community. This fact is probably the result of their inability to utilize current Chemical Abstracts nomenclature, wherein most literature references to metal hydrides appear. Metal hydrides function by transfer of a hydride to the electron-deficient center (typically carbon) of a double bond. Protonation is effected on the electron rich center via the solvent media in the case of NaBH_4 or product work-up in case of LiAlH_4 .

The infrequent use of metal hydride reducing agents in clandestine laboratories cannot be attributed to the lack of open literature references in these agents [55–62]. Methamphetamine has been produced in clandestine laboratory sites via NaBH_4 reduction of the Schiff Base adduct of P-2-P and methylamine following a procedure outlined by Weichet et al. [55] (Fig. 2). Unfortunately, the activity of NaBH_4 is sufficient to reduce the ketone of P-2-P and this is a competing reaction. This is not the case with the more selective reducing agent NaCNBH_3 , whose activity is dependent on the pH of the reaction media [57]. Lithium aluminum hydride, whose activity is greater and therefore less selective than NaBH_4 , has been used to produce methamphetamine or amphetamine through the reduction of a variety of functional groups; i.e. formyl [58] (Fig. 8), carbamate [59] (Fig. 10), oxime [60] (Fig. 3), nitrostyrenes [61] (Fig. 4) and halogen analogs [62] (Fig. 11). Sodium borohydride has also been used in a demercuration procedure route followed by acid hydrolysis to amphetamine (in a clandestine laboratory) as outlined in Fig. 12 [56].

Non-metal reductions

Non-metal reduction routes to methamphetamine and amphetamine have been what might be termed as “fads” in clandestine laboratory synthesis within the United States. In the early and mid 1970s, the Leuckart Synthesis, which employs formic acid, was the most popular clandestine route to amphetamine and methamphetamine. For whatever reason, this route, which is still very common in Western Europe, lost popularity in the United States by the end of the 1970s. In the early 1980s, the hydriodic acid reduction of ephedrine to methamphetamine began increasing in frequency in the Southwestern and Western areas of the United States. Although several literature references link the Leuckart synthesis (Fig. 8) to amphetamine [67–69] and methamphetamine [64–66], “no” open literature reference directly links

hydriodic acid reduction of a benzylic alcohol to the production of methamphetamine (Fig. 1). Several general benzylic alcohols have been reduced to their aliphatic counterparts [63]. However, this 'cross application' of chemical syntheses would require a level of chemical knowledge not common among clandestine chemists.

The mechanism of the Leuckart reaction has been studied [65,71,72] and shown to be a free radical process initiated by formic acid. Unfortunately, the mechanism of the hydriodic acid reduction has not been established. It seems clear that the benzylic alcohol of ephedrine undergoes a substitution reaction with iodine. However, the mechanism of the carbon-halogen reduction is in conjecture; i.e. hydride transfer, internal electrolysis via disproportionation of iodine, or elevated temperature decomposition of HI to H₂ and I₂ whereby H₂ reduces the C-I bond [63].

Conclusion

In this review we have addressed reductive approaches to amphetamine and methamphetamine via heterogeneous catalysis, dissolving metals, metal hydrides and non-metal reductions. The chemistry of these varied approaches has been highlighted with emphasis on the role of the reducing species. It may be concluded that there are many options available to clandestine chemists (see Figs. 1–12). However, in actual practice, the three most frequently encountered routes in the United States are (1) the aluminum foil reduction of the Schiff Base adduct of P-2-P and methylamine [40–44], (2) the palladium catalyzed reduction of the chloro analog of ephedrine to methamphetamine [4,5] and (3) the hydriodic acid reduction of ephedrine to methamphetamine [63; pers. comm.*].

References

- 1 A. Sinnema and A.M.A. Verweji, Impurities in illicit amphetamine: A review. *Bull. Narc.*, Vol. XXXIII, no. 3 (1981) 37–54.
- 2 C.L. Hider, Preparation of evidence in illicit amphetamine. *J. Forensic Sci.*, 9 (1969) 75–79.
- 3 Pd, Figure 1.
Ephedrine with HCl (gas) reduced to methamphetamine
H. Metzger, Bases of the 1-phenyl-2-aminopropane series. German Patent No. 968,545 Mar. 6, 1958. C.A. 54: 7654b (1960).
- 4 Pd, Figure 1.
Chloro ephedrine reduced to methamphetamine
A. Gero, Some reactions of 1-phenyl-1-chloro-2-methylaminopropane. I. Reaction with metals and hydrogen. *J. Org. Chem.*, 16 (1951) 1731–1735. C.A. 46: 6606g (1952).
- 5 Pd/BaSO₄, Figure 1.
Bromo or chloro ephedrine reduced to methamphetamine
H. Emde, Concerning diastereoisomers I. Configuration of ephedrine. *Helv. Chem. Acta*, 12 (1929) 365–376. C.A. 23: 3452–3454 (1929).

*J. Heagy, pers. commun. from information gathered by attending clandestine laboratory sites. Drug Enforcement Administration, 450 Golden Gate Avenue, San Francisco, CA 94102, U.S.A.

- 6 Pd and Pt, Figure 1.
Ephedrine ester reduced to methamphetamine
W. Dobke and F. Keil, Amines. British Patent No. 509,661, Oct., 3, 1938. C.A. 34: 3761 (1940).
- 7 Pd/C, Figure 1.
Ephedrine phosphate ester reduced to methamphetamine
A. Larizza, G. Brancaccio and A. Segre, l-, d- and d,l-Ephedrine phosphates. *J. Med. Chem.*, 9 (1966) 996–997. C.A. 66: 28945y (1967).
- 8 Pd/BaSO₄, Figure 1.
Ephedrine with perchloric acid reduced to methamphetamine
K.W. Rosenmund, E. Karg and F.K. Marcus, Concerning the preparation of beta-Aryl-Alkylamines. *Berichte*, 75B (1942) 1850–1859. C.A. 38: 1219 (1944).
- 9 Pd/C, Figure 2.
Schiff base reduced to methamphetamine
American Home Products Corp. Imines. British Patent No. 702,985, Jan. 27, 1954. C.A. 49: 5515g (1955).
- 10 Pd, Figure 2.
Schiff base (P-2-P + MeNH₂) reduced to methamphetamine
M. Tsutsumi, An illegal preparation of an amphetamine-like compound. *Science Crime Detect.*, (Japan) 6 (1953) 50–52. C.A. 47: 11661h (1953).
- 11 Pd/HCl
Chloro analog of phenylpropanolamine to amphetamine
W.H. Hartung and J.C. Munch, Amino Alcohols. VI. The preparation and pharmacodynamic activity of four isomeric phenylpropylamines. *J. Am. Chem. Soc.*, 53 (1931) 1875–1879. C.A. 25: 3635 (1931).
- 12 Pd/C
Nitrile reduction to phenethylamines
W.H. Hartung, Catalytic reduction of nitriles and oximes. *J. Am. Chem. Soc.*, 50 (1928) 3370–3374. C.A. 23: 599 (1929).
- 13 Pd and Pt with a slurry of Ni, Figure 4.
Nitrostyrene reduction to amphetamine
L.A. Bryan, Hydrogenation of 1-phenyl-2-nitropropene to alpha-methylphenethylamines. U.S. Patent No. 3,456,576. C.A. 71: 91049c (1969).
- 14 Pd, Figure 3.
Oxime reduction to amphetamine
K. Kindler, B. Hedemann and E. Scharfe, A study of mechanisms of chemical reactions. X. Phenyl and cyclohexyl-alkylamine by hydrogenation. *Justus Liebigs Ann. Chem.*, 560 (1948) 215–221. C.A. 43: 1025h (1949).
- 15 Pd/C, Figure 1.
Pseudoephedrine reduced to methamphetamine
H. Temmler, Amines, French Patent No. 844,227 July 20, 1939. C.A. 34: 7297¹ (1940).
- 16 Pd/C, Figure 5.
2-keto oxime reduction to phenylpropanolamine
W.H. Hartung and Y. Chang, Palladium catalysis. IV. Change in behavior of palladium-charcoal in hydrogenation reactions. *J. Am. Chem. Soc.*, 74 (1952) 5927–5929. C.A. 48: 115g (1954).
- 17 Pd/C, Figure 1.
Ephedrine reduction to methamphetamine
K. Kindler, B. Hedemann and E. Scharfe, Study of mechanisms of chemical reaction. X. Phenyl and cyclohexyl-alkyl amines by hydrogenation. *Justus Liebigs Ann. Chem.*, 560 (1948) 215–221. C.A. 43: 1025g (1949).
- 18 Pt, Figure 1.
Chloroephedrine reduction to methamphetamine
W. Dobke and F. Keil, Amines. German Patent No. 767,186, Jan. 31 (1952). C.A. 49: 1598c (1955). British Patent No. 509,661, Oct. 3 (1938). C.A. 34: 3761 (1940).

- 19 Pt, Figure 1
Chloroephedrine reduction to methamphetamine
S. Nakajima, 1-Phenyl-2-methylaminopropane, Japanese Patent No. 2307 (1951), May 15 (1951). C.A. 47: 5437h (1953).
- 20 Pt, Figure 2
Schiff base reduction (P-2-P + NH_3) to amphetamine
E.R. Alexander and A.L. Misegades, A low pressure reductive alkylation method for the conversion of ketones to primary amines. *J. Am. Chem. Soc.*, 70 (1948) 1315–1316. C.A. 42: 5411d (1948).
- 21 Pt or activated Al, Figure 2
Schiff base reduction (P-2-P + MeNH_2) to methamphetamine
D. Shiho, A new process of alkylation of amines. *J. Chem. Soc. Jpn.*, 65 (1944) 237–239. C.A. 41: 3799i (1947).
- 22 Pt, Figure 2.
Schiff base reduction (P-2-P + MeNH_2) to methamphetamine
W. Dobke and F. Keil, *beta*-Arylalkylamines. French Patent No. 844,227 C.A. 34: 7297^s (1940). German Patent No. 767,263 (1952). C.A. 47: 2772c (1953).
- 23 Pt/C also Ni and Al, Figure 6.
Phenylacetone hydrazones reduction to amphetamine
T.H. Temmler, Reduction to hydrazones. German Patent No. 870,265 Mar.12 (1953). C.A. 52: 16301d (1958).
- 24 Pt, Figure 5.
2-keto oxime reduced to ephedrine
R.H.F. Manske and T.B. Johnson, Synthesis of ephedrine and structurally similar compounds. I. *J. Am. Chem. Soc.*, 51 (1929) 580–582. C.A. 23: 1404 (1929).
- 25 CuO, CaSO₄, BaSO₄, Figure 2.
Schiff base reduction (P-2-P + MeNH_2) to methamphetamine
J.B. Tindall, Process for the production of secondary amines. U.S. Patent No. 2,828,343, Mar. 25, 1958. C.A. 52: 13775f (1958).
- 26 Ni-Al, Figure 2.
Schiff base reduction (P-2-P + NH_3) to amphetamine
P. Mastigle, M. Metayer and A. Bricard, Study of the aminolysis of some ketones and aldehydes. *Bull. Soc. Chim. France* (1950) 1045–1048. C.A. 45: 8970h (1951).
- 27 Ni-Al, Figure 2.
Schiff base reduction (P-2-P + NH_3) to amphetamine
L. Haskelberg, Aminative reduction of ketones. *J. Am. Chem. Soc.*, 70 (1948) 2811–2812. C.A. 43: 1349f (1940).
- 28 Ni-Al, Figure 2.
Schiff base reduced (P-2-P + NH_3) to amphetamine
A. Novelli, Sympathicomimetics, preparation of nitrogen-substituted *beta*-phenylisopropylamines. *Anal. Assoc. Quim. Argentina* 27 (1939) 169–171. C.A. 34: 1627^s (1940).
- 29 Ni-Al, Figure 2.
Schiff base reduced (P-2-P + NH_3) to amphetamine
M. Green, Reductive amination of ketones. U.S. Patent No. 3,187,047, June 1, 1965. C.A. 63: 9873f (1965).
- 30 Ni-Al, Figure 3.
Oxime reduced to amphetamine
J.W. Wilson, Synthesis of dl-amphetamine sulfate labeled with C¹⁴. *J. Am. Pharm. Assoc.*, (Sci. Ed.), 39 (1950) 687. C.A. 45: 1728d (1951).
- 31 Ni-Al, Figure 3.
Oxime reduced to amphetamine
T. Kametani and Y. Nomura, Reduction of nitrogen compounds by Raney nickel alloy and alkali solution. I. *J. Pharm. Soc. Jpn.*, 74 (1954) 413–416. C.A. 49: 5342d (1955).

- 32 Ni-Al, Figure 4.
Nitrostyrene reduced to amphetamine
J.B. Tindall, Reduction of nitro olefins. U.S. Patent No. 2,636,901, Apr. 28, 1953. C.A. 48: 2771f (1954).
- 33 Ni-Al, Figure 4.
Nitrostyrene reduced to amphetamine
G. Stochdorph and O. Schickh, Saturated amines. German Patent No. 848,197, Sept. 1, 1952. C.A. 47: 5438b (1953).
- 34 Ni-Al, Figure 6.
Hydrazone reduced to amphetamine
R. Fusco and L. Canonica, Reduction of phenylhydrazone-p-sulfonic acids. *Chim. Ind. (Milan)*, 32 (1950) 208–210. C.A. 45: 4645a (1951).
- 35 Ni-Al, Figure 3.
Oxime reduction to amphetamine
H.B. Hass, A.G. Susie and B.L. Heider, Nitroalkane derivatives. *J. Org. Chem.*, 15 (1949) 8–14. C.A. 44: 4412d (1950).
- 36 Ni-Al, Figure 5.
2-keto oxime reduced to phenylpropanolamine
P.L. Cook, The reduction of aldehydes and ketones with nickel-aluminum alloy in aqueous alkaline solution. *J. Am. Chem. Soc.*, 27 (1962) 3873–3875. C.A. 58: 464c (1963).
- 37 Ni-Al
Chloroephedrine reduced to methamphetamine
W. Leithe, Configuration of the ephedrine bases. *Berichte*, 65 (1932) 660–666. C.A. 26: 3495.
- 38 Ni-Al, Figure 5.
2-Keto oxime reduced to phenylpropanolamine
V. Evdokimoff, Reduction reaction with nickel-aluminum alloy. Applications to the synthesis of norephedrine and of other pharmacologically active amines. *Gazz. Chim. Ital.*, 81 (1951) 725–734. C.A. 46: 7070d (1952).
- 39 CaH_2 -Pd, HCl, Figure 1.
Chloroephedrine reduced to methamphetamine
A. Gero, Some reactions of 1-phenyl-1-chloro-2-(methylamino)propane I. Reaction with metals and with hydrogen. *J. Org. Chem.*, 16 (1951) 1731–1736. C.A. 46: 6606g (1952).
- 40 Al-Hg, Figure 2.
Schiff base reduced ($\text{P-2-P} + \text{MeNH}_2$) to methamphetamine
Laboratoires Amido, French Patent No. M2782, Oct. 5, 1964. C.A. 62: 5228b (1965).
- 41 Al-Hg, Figure 2.
Schiff base reduced ($\text{P-2-P} + \text{MeNH}_2$) to methamphetamine
F. Keil and W. Dobke, N-Monomethyl-beta-phenylamines, German Patent No. 871,155, Mar. 19, 1953. C.A. 52: 20055e (1958); British Patent No. 508,756, C.A. 34: 776^s (1940).
- 42 Al-Hg, Figure 2.
Schiff base reduced ($\text{P-2-P} + \text{MeNH}_2$) to methamphetamine
D. Shiho, A new process of alkylation of amines. *J. Chem. Soc. Jpn.*, 65 (1944) 135–140. C.A. 41: 3800c (1947).
- 43 Al-Hg, Figure 2.
Schiff base reduced ($\text{P-2-P} + \text{MeNH}_2$) to methamphetamine
H Temmler, Amines. French Patent No. 844,288, July 20, 1939. C.A. 34: 7544^r (1940).
- 44 Al-Hg, Figure 2.
Schiff base reduced ($\text{P-2-P} + \text{NH}_3$) to amphetamine
B.H.G. Wassink, A. Duijndam and A.C.A. Jansen, A synthesis of amphetamine. *J. Chem. Ed.*, 51 (1974) 671. No C.A. citation.
- 45 Al-Hg, Figure 6.
Hydrazone reduction to amphetamine
T.H. Temmler, Reduction of hydrazones. German Patent No. 870,265, Mar. 12, 1953. C.A. 52: 16301d (1958).

- 46 Na/Alc, Figure 2.
Schiff base reduced (P-2-P + MeNH₂) to methamphetamine
A. Ogata, Constitution of ephedrine. Desoxyephedrine. *J. Pharm. Soc. Jpn.*, 451 (1919) 751–764. C.A. 14: 745 (1920).
- 47 Na/Alc, Figure 9.
alpha-Bromobenzyl Methyl ketone + Thioformamide = 5-Phenyl-4-methylthiazole + Na/Alc to methamphetamine
H. Erlenmeyer and M. Simon, Investigation in structure chemistry VI. Concerning a reductive cleavage of 5-phenyl-4-methylthiazole. *Helv. Chim. Acta*, 25 (1942) 528–530. C.A. 36: 6539⁶ (1942).
- 48 Na/Alc, Figure 3.
Oxime reduced to amphetamine
F.M. Jaeger and J.A. van Dijk, Preparation of 2-phenylisopropylamine. *Proc. Acad. Sci. Amsterdam*, 44 (1941) 26–40. C.A. 37: 621⁹ (1943).
- 49 Na/Alc, Figure 3.
Oxime reduced to amphetamine.
W. Leithe, Configuration of ephedrine bases. *Berichte*, 65 (1932) 660–666. C.A. 26: 3495 (1932).
- 50 Na-Hg, Figure 4.
Nitrostyrene reduced to amphetamine
G.A. Alles, Salts of 1-phenyl-2-aminopropane. U.S. Patent No. 1,879,003, Sept. 1932. C.A. 27: 373 (1933).
- 51 Na-Hg, Figure 3.
Oxime reduced to amphetamine
D.H. Hey, dl-Phenylisopropylamine and related compounds. *J. Chem. Soc.* (1930) 18–21. C.A. 24: 1851 (1930).
- 52 Fe, HCl, Figure 4.
Nitrostyrene reduced to phenyl-2-propanone
H.B. Hass, A.G. Susie and R.L. Heider, Nitro-alkane derivatives. *J. Org. Chem.*, 15 (1950) 8–14. C.A. 44: 4412d (1950).
- 53 Fe, HCl, Figure 4.
Friedel Crafts followed by nitrostyrene reduction and hydrolysis to phenyl-2-propanone (all in situ) R.V. Heinzelman, Alkyl arylalkyl ketones. U.S. Patent No. 2,557,051 (1951) C.A. 46: 531g (1952).
- 54 Zn, HCl, Figure 1.
Zn-Cu, HCl
Zn-Pd, HCl
Zn-Cu-Pd, HCl
Chloroephedrine reduced to methamphetamine
A. Gero, Some reactions of 1-phenyl-1-chloro-2-(methylamino)-propane. I. Reactions with metals and with hydrogen. *J. Org. Chem.*, 16 (1951) 1731–1735. C.A. 46: 6606g (1952).
- 55 NaBH₄
Schiff base reduced (ketone + MeNH₂) to ephedrine
J. Weichet, J. Hodrova and L. Blaha, Reductive amination of phenylacetylcarbinols by sodium borohydride. *Coll. Czech. Chem. Commun.*, 26 (1961) 2040–2044. C.A. 56: 5864c (1962).
- 56 NaBH₄, Figure 12.
Demercuration followed by acid hydrolysis to amphetamine.
H.C. Brown and J.T. Kurek, Solvomercuration-demercuration of representative olifins in the presence of acetonitrile. Convenient procedure for the synthesis of amines. *J. Am. Chem. Soc.*, 91 (1969) 5647–5649. C.A. 71: 101261g (1969).
- 57 NaCNBH₄, Figure 2.
(Ketone + Amine) reduced to amines.
R.F. Borch, M.D. Bernstein and H.D. Durst
The Cyanohydridoborate anion as a selective reducing agent. *J. Am. Chem. Soc.*, 93 (1971) 2897–2904. C.A. 75: 49525n (1971).

- 58 LiAlH_4 , Figure 8.
N-formylamphetamine reduced to methamphetamine
O. Cervinka, E. Kroupova and O. Belovsky, Asymmetric reactions. XXIX. Absolute configuration of phenyl-2-alkylamines and their N-methyl derivatives. *Coll. Czech. Chem. Commun.*, 33(11) (1968) 3551–3557. C.A. 70: 37323d (1969).
- 59 LiAlH_4 , Figure 10.
d-Phenylalanine carbamate reduced to amphetamine
R.B. Repke, D.K. Bates and W.J. Ferguson, Synthesis of dextroamphetamine sulfate and methamphetamine hydrochloride from d-phenylalanine. *J. Pharm. Sci.*, 67 (1978) 1168–1169. C.A. 89: 163164h (1978).
- 60 LiAlH_4 , Figure 3.
Oxime reduced to amphetamine
K. Kotera, T. Okada and S. Miyazaki, Stereochemistry of aziridine formation by reduction of oximes with lithium aluminium hydride on arylalkyl alkyl ketoximes and their tosylates. *Tetrahedron*, 24 (1968) 5677–5690. C.A. 69: 67158a (1968).
- 61 LiAlH_4 , Figure 4.
Nitrostyrene reduced to amphetamine
R.T. Gilsdorf and F.F. Nord, Reverse addition of lithium aluminum hydride to nitroolefins. *J. Am. Chem. Soc.*, 74 (1952) 1837–1843. C.A. 48: 553c (1954).
- 62 LiAlH_4 , Figure 11.
1-Phenyl-2-amino-3-iodopropane to amphetamine (2,2-dimethyl-5-amino-6-phenyl-1,3-dioxane + HI + P in $\text{HOAc}/\text{Ac}_2\text{O}$ = 1-phenyl-2-amino-3-iodopropane)
K. Shinohara, M. Tamura and T. Hosoda, 1-Phenyl-2-aminopropanes. Japan Patent No. 10,914 (1964) June 17, 1961. C.A. 61: 11930cd (1964).
- 63 HI, Figure 1.
Reduction of a benzylic alcohol (General)
(a) T. Ho and C.M. Wong, *Synthesis* 161 (1975). (b) W.E. Parkam and Y.A. Sayed, *Synthesis*, 116 (1976). (c) K.N.F. Shaw, M.D. Armstrong and A. McMillan, *J. Org. Chem.*, 21 (1956) 1149–1151. (d) A.C. Cope et al., *J. Am. Chem. Soc.*, 84 (1962) 2170. (e) W. Reusch and R. LeMahiem, *J. Am. Chem. Soc.*, 86 (1964) 3068. (f) C.S. Marvel, F.D. Hager and E.C. Caudle, *Org. Synth., Coll.*, Vol. I, 224–225. © 1941.
- 64 HCOOH , Figure 8.
Ketone + HCONHCH_3 = formyl + HCl to amine
A.I. Vogel, *Textbook of Practical Organic Chemistry*, 4th ed. (Longman Scientific and Technical) New York, 1987. pp. 568–569.
- 65 HCOOH , Figure 8.
Leuckart mechanism study and synthesis of amphetamine
F.S. Crossley and M.L. Moore, Studies on the Leuckart reaction. *J. Org. Chem.*, 9 (1944) 529–536. C.A. 39: 1147⁶ (1945).
- 66 HCOOH , Figure 8.
Leuckart to N-formylamphetamine followed by LiAlH_4 reduction to methamphetamine
O. Cervinka, E. Kroupova and O. Belovsky, Asymmetric Reactions. XIX. Absolute configuration of 1-phenyl-2-alkylamines and their N-methyl derivatives. *Coll. Czech. Chem. Commun.*, 33(11) (1968) 3551–3557. C.A. 70: 37323d.
- 67 HCOOH , Figure 8.
Leuckart to amphetamine
O.Y. Magidson and G.A. Garkuska, Synthesis of beta-phenyl-isopropylamine. *J. Gen. Chem. (U.S.S.R.)*, 11 (1941) 339–343. C.A. 35: 5869⁶ (1941).
- 68 HCOOH , Figure 8.
Leuckart to amphetamine
B.R. Bobranskii and Y.K. Drabik, A new method of 1-phenyl-2-aminopropane preparation. *J. Appl. Chem. (U.S.S.R.)*, 14 (1941) 410–414. C.A. 36: 2531⁶.

- 69 HCOOH, Figure 8.
Leuckart reaction to amphetamine and methamphetamine
A. Ogata, *alpha* and *beta*-Aminoalkyl(aryl)benzenes and their derivatives. *J. Pharm. Soc. Jpn.*, 445 (1919) 193–216. C.A. 13: 1709 (1919).
- 70 HCOOH, Figure 8.
Leuckart mechanism study
M.L. Moore, The Leuckart reaction. *Org. React.*, 5 (1949) 301–330. C.A. 44: 553c (1950).
- 71 HCOOH, Figure 8.
Leuckart mechanism study
E.R. Alexander and R.B. Wildman, Studies on the mechanism of the Leuckart reaction. *J. Am. Chem. Soc.*, 70 (1948) 1187–1189. C.A. 42: 7263e (1948).
- 72 HCOOH, Figure 8.
Leuckart mechanism study
A. Lukaszewicz, The mechanism of the Leuckart-Wallach reaction and of the reduction of Schiff bases by formic acid. *Tetrahedron*, 19 (1963) 1789–1799. C.A. 60: 1549f (1964).
- 73 P-2-P via Phenylacetic acid and Ac_2O
O.Y. Magidson and G.A. Garkusha, Synthesis of phenyl-isopropylamine (Phenamine). *J. Appl. Chem. (U.S.S.R.)*, 11 (1941) 339–343. C.A. 35: 5868^s (1941).
- 74 P-2-P via phenylacetic acid and lead acetate
M. Tsutsumi, An illegal preparation of an amphetamine-like compound. *Science Crime Detect.* (Japan), 6 (1953) 50–52. C.A. 47: 11661h (1953).
- 75 P-2-P via phenylacetic acid and ThO_2 or MgO
A.I. Vogel, *A Textbook of Practical Organic Chemistry*, 1st Edition (Longmans, Green and Co.), 1948, London, pp. 698–700 and 336–338.
- 76 P-2-P via phenylacetic acid and ThO_2
R.M. Herbst and R.H. Manske, Methyl benzyl ketone (phenylacetone). *Org. Synth.*, 16 (1936) 47–50. C.A. 30: 3807 (1936) *Org. Synth. Coll.*, Vol. II (1943) 389–391.
- 77 Phenylacetic acid via benzylocyanide or Grignard
A.I. Vogel, *Textbook of Practical Organic Chemistry*, 1st Edition (Longmans, Green and Co.) London, 1948, pp. 722–723 and 727–728.
- 78 P.L. Julian, J.J. Oliver, R.H. Kimball, A.B. Pike and G.D. Jefferson, 2-Phenylacetoacetonitrile (acetobenzyl cyanide). *Org. Synth.*, 18 (1944) 54–55 and 66–69. C.A. 36: 2531 (1942). *Org. Synth. Coll.*, Vol. II (1943) 487–489.
- 79 B.R. Bobranski and Y.V. Drabik, A new method of 1-phenyl-2-aminopropane preparation. *J. Appl. Chem. (U.S.S.R.)*, 14 (1941) 410–414. C.A. 36: 2531 (1942).
- 80 J.W. Wilson, Synthesis of dl-amphetamine sulfate labeled with C^{14} . *J. Am. Pharm. Assoc. (Sci. Ed.)*, 39 (1950) 687. C.A. 45: 1728d (1951).
- 81 H.G. Walker and C.R. Hauser, Synthesis of methyl ketones from diethyl acylmalonates. *J. Am. Chem. Soc.*, 68 (1946) 1386–1388. C.A. 40: 5712 (1946).
- 82 E.H. Sund and H.R. Henze, Alkyl benzyl ketones and hydantoin derivatives. *J. Am. Chem. Eng. Data*, 15 (1970) 200.
- 83 A. McKillop and J.D. Hunt, Thallium in organic synthesis. XX. Oxidative rearrangement of olefins with thallium (III) nitrate: A simple one-step synthesis of aldehydes and ketones. *Tetrahed. Lett.*, 60 (1970) 5275.
- 84 M. Tiffeneau, Transformation of magnesium derivatives of chlorhydrins. *Ann. Chim. Phys.*, 10 (1907) 322–378. C.A. 2: 265 (1908).
- 85 J.P. Mason and L.I. Terry, Preparation of phenylacetone. *J. Am. Chem. Soc.*, 62 (1940) 1622. C.A. 34: 6248^s (1940).
- 86 J.A. King and F.H. McMillan, The decarboxylative acylation of arylacetic acids. *J. Am. Chem. Soc.*, 73 (1951) 4911–4915. C.A. 47: 535a (1953).
- 87 F.A. Carey and R.J. Sundberg, *Advanced Organic Chemistry*, Part B. Plenum Press, New York, N.Y., 1977.
- 88 C.B. Lebrilla and W.F. Maier, C-H Activation on platinum, a mechanistic study. *J. Am. Chem. Soc.*, 108 (1986) 1606–1616.

- 89 W.F. Maier, S.J. Chettle, R.S. Rai and G. Thomas, Metamorphosis of palladium and its relation to selectivity in the Rosenmund reaction. *J. Am. Chem. Soc.*, 108 (1986) 2608–2616.
- 90 H.O. House, *Modern Synthetic Reductions*, second ed. Benjamin/Cummings Publishing Co., Philippines, 1972.
- 91 D.A. Cooper, Mass spectrometry in the forensic sciences. *Spectra*, 10 (1985) 3–10.
- 92 F.T. Noggle, Jr., J. DeRuiter and C.R. Clark, Liquid chromatographic determination of the enantiomeric composition of methamphetamine prepared from ephedrine and pseudoephedrine. *Anal. Chem.*, 58 (1986) 1643–1648.
- 93 A.C. Allen and W.O. Kiser, Methamphetamine from ephedrine: I. Chloroephedrine and aziridines. *J. Forensic Sci.*, 32 (1987) 953–962.