Nickel–Aluminum Alloy as a Reducing Agent

LARRY K. KEEFER*

Chemistry Section, Laboratory of Comparative Carcinogenesis, National Cancer Institute, Frederick Cancer Research Facility, Frederick, Maryland 21701

GEORGE LUNN*

Environmental Control and Research Program, Program Resources, Inc., National Cancer Institute, Frederick Cancer Research Facility, Frederick, Maryland 21701

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I. Introduction

Raney nickel and related catalysts[1-5] have become enormously valuable agents for inducing chemical transformations in the research laboratory as well as on the commercial scale. The literature documenting their applications is voluminous, and there are numerous reviews available as guides to their synthetic utilization.[5-8]

What is not so well-known is that the alloys of aluminum with nickel and other transition metals from which the Raney catalysts are prepared are themselves extremely useful reducing agents. This fact was recognized by several groups soon after the alloys became commercially available, and vigorous development work pursued during the 1940s and 1950s revealed their considerable potential in organic synthesis.[8-10] During the 1960s and 1970s, however, the use of nickel–aluminum alloy as a reducing agent was strangely ignored,

with only a few expansions of the method's scope being reported in those decades. Indeed, the technique was the subject of so little comment in the literature during that time that one group recently referred to it as "forgotten".[11] Nevertheless, the past few years have seen a renaissance of interest in the area, with extensions of the methodology to a variety of new problem types and previously unstudied functional groups being described.

The purpose of this review is to illustrate the many applications of nickel–aluminum alloy (but not of Raney catalyst per se) as a reductant that have been reported since 1937. Our goal in doing so is to stimulate renewed and general awareness of the important advantages to be gained by using this "forgotten" technique.

II. Nature of the Reductant and Its Action

The reducing agent that is the subject of this review is an alloy consisting of roughly equal portions by weight of aluminum and nickel.[5] Its preparation has been described in the original patents[1-4] by Murray Raney as well as in subsequent reviews.[5-8] It can be purchased through several suppliers.[12] Manufacturer's literature[13,14] identifies the material produced by W. R. Grace & Co., Davison Chemical Division, as Raney Alloy 2813, Nickel–Aluminum Alloy Powder, consisting of 50–52% aluminum, 48–50% nickel, and traces (0.2–0.3%) of iron.[15] It is a gray powder with a mean particle size of $\sim$65 μm.[13,15] It is insoluble in water, but its slurries are slightly alkaline and react slowly with the solvent to evolve hydrogen. It is stable to storage in air.[13]

To use nickel–aluminum alloy as a reductant, it is only necessary to sprinkle it into a suitable hydroxylic medium containing the substance to be reduced.[16,17] The solvent is usually an aqueous solution of an alkali-metal hydroxide at a concentration of 0.1 M or greater, but mixtures of water with formic acid[18] or of aqueous alkali with organic solvents have often proven advantageous. Reductions have even been carried out in pure water.[19,23] Many workers have heated these reaction mixtures on the steam bath, but this does not generally appear to be necessary. Reactions can often be performed by stirring the ingredients at room temperature, although the exothermic nature can elevate the temperature appreciably after an induction period.

Mechanistically, the reaction is initiated with the attack of the hydroxylic solvent on the aluminum,
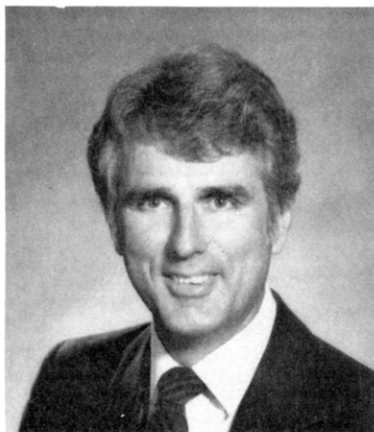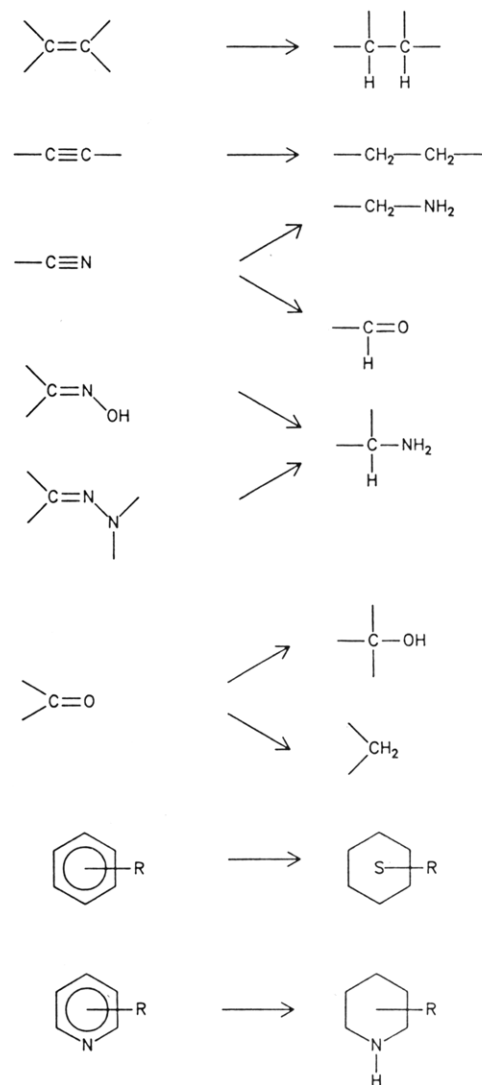
Larry Keefer was born in Akron, OH, in 1939. He received his A.B. in 1961 from Oberlin College and his Ph.D. in Organic Chemistry in 1965 with Gloria Lyle at the University of New Hampshire. His career since then has been devoted entirely to research on the chemistry of nitrosamines and other carcinogens, first at the Chicago Medical School, then from 1968 to 1971 at the University of Nebraska College of Medicine, and most recently at the National Cancer Institute (NCI). Currently Chief of the Chemistry Section in the NCI's Laboratory of Comparative Carcinogenesis, he is studying mechanisms of carcinogen formation (to learn how to prevent the introduction of these hazardous compounds into the environment), the chemical reactivity of carcinogens (to determine how they can be destroyed before human exposure can occur—the original source of our interest in nickel–aluminum alloy as a reducing agent), and the carcinogens' mechanisms of biological action (with the aim of devising strategies for protecting victims of unavoidable exposure from their tumorigenic effects).
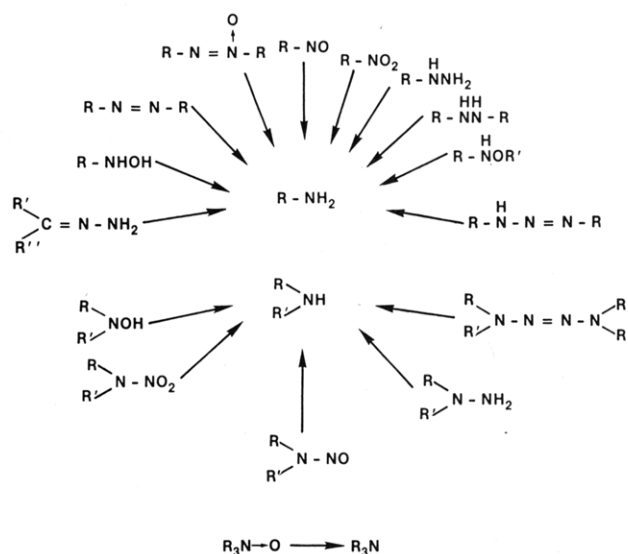
George Lunn was born in Worthing, England, in 1950. He received his B.Sc. in 1972 and his Ph.D. in Organic Chemistry in 1975 from the University of Edinburgh. His thesis supervisor was Professor J. I. G. Cadogan. He was a NATO postdoctoral fellow with Professor Barry Trost at the University of Wisconsin, Madison, and a Royal Commission for the Exhibition of 1851 fellow with Professor R. C. Cookson at the University of Southampton before joining the National Cancer Institute, Frederick Cancer Research Facility, in 1980. His research interests include improving laboratory safety by the chemical destruction of hazardous compounds and the use of nickel–aluminum alloy as a reducing agent for organic compounds.
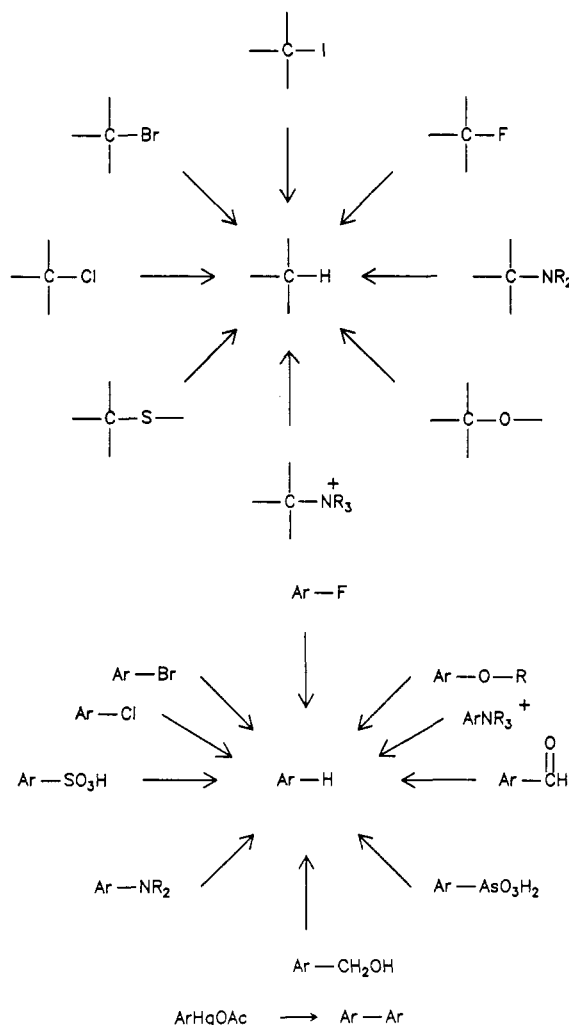

Figure 1. Some unsaturated compound types that have frequently been hydrogenated by mixing with nickel–aluminum alloy in hydroxylic media.

Figure 2. Functional groups containing N–N and/or N–O bonds cleaved with nickel–aluminum alloy and base.

forming aluminate ion in basic media with the concurrent generation of hydrogen gas and spongy nickel. It is the latter two reagents that are mixed to effect a classical Raney nickel reduction, so the alloy–base reducing combination is in part a typical Raney catalyst–hydrogen system in which the H_2 is activated for the reduction by adsorption on the finely divided $(80–100 \text{ m}^2/\text{g})^{14}$ catalytic surface. It is important to recognize, however, that the dissolution of aluminum in alkali also generates a powerful reducing action,[21] so the technique has the characteristics of a dissolving-metal reduction as well. As such, it can be considered an important example of a reaction type known as

"heterogeneous catalytic transfer hydrogenations" that has recently been reviewed.[22] Usable Raney nickel catalysts can often be isolated as byproducts of reac-

In this section, results with each type of functional group are illustrated with specific examples from the literature.

A. Hydrogenations

1. Carbon–Carbon Double and Triple Bonds

As documented in Table I, most carbon–carbon double bonds are easily saturated by mixing with nickel–aluminum alloy in base.[16,17,20,24-52] Entries I-1 and I-17 offer support for this generalization, although several exceptions have been reported (e.g., reactions I-27 and I-55). A typical example that has been described in detail as an *Organic Syntheses* preparation is the conversion of o-carboxycinnamic acid to its dihydro derivative, as summarized in reaction I-15. This transformation illustrates several characteristics of nickel–aluminum alloy as a reducing agent. The double bond is reduced almost quantitatively simply by warming the starting material with the alloy at atmospheric pressure in 10% sodium hydroxide solution for 1–2 h, without the need for a preformed catalyst or a hydrogenation apparatus. The aryl ring is not reduced under these conditions, though more vigorous treatment can sometimes hydrogenate carbocyclic and heterocyclic aromatic compounds, as discussed in the next section. The carboxylate moieties are not affected by this treatment; this appears to be a general rule, as numerous reductions of carboxylic acids containing C=C double bonds elsewhere in the molecule have hydrogenated the latter while leaving the former functional group intact.

Example I-7 suggests that inertness to reduction by nickel–aluminum alloy in base is also a property of the carboxamide function. N-Methyl-2-pyridone added four hydrogen atoms to the ring's C=C bonds but left the resulting lactam moiety unchanged.

Unsaturated esters can be hydrolyzed during hydrogenation. Examples I-28 and I-30 illustrate the different possible outcomes. In I-28, the hydrogenated and hydrolyzed product was observed in 93% yield, while in I-30 the α,β-unsaturated lactone was converted to the dihydro derivative without hydrolysis in 85% yield.

The stereochemistry of reduction usually involves cis addition of hydrogen, as might be expected for a reducing system with characteristics of a catalytic hydrogenation. Reactions I-24 and I-25 are cases in point. In both examples, cis olefins are reduced to meso products. Trans addition has also been reported, however, as discussed below.

While the majority of olefin reductions reported in the literature have involved starting materials that contain enol, phenol, carboxylic acid, or other functional groups expected to promote reactant solubility in the basic medium, this is by no means a requirement. Even unsaturated hydrocarbons that are not otherwise functionalized, such as cyclooctatetraene (reaction I-27), can be reduced successfully in excellent yield.

Reaction I-27 also illustrates the point that, while most double bonds are rapidly and efficiently reduced with nickel–aluminum alloy in aqueous alkali, some may be resistant to hydrogenation. In this case, three double bonds were saturated with ease, but the fourth remained unaffected, leaving cyclooctene as the sole product in 90–95% yield. Another example of the de-

Figure 3. Reported hydrogenolyses of aryl C–S, C–halide, C–O, C–N, C–C, C–As, and C–Hg bonds using nickel–aluminum alloy in base.

tions in which the alloy is the reductant.[15] Preliminary work has suggested that after the aluminum and hydrogen have been consumed, the catalytic activity of the nickel produced in these reactions can be exploited to achieve further reductions by addition of either aluminum foil or an atmosphere of hydrogen to the reaction mixture.[23]

III. Applications by Functional Group

Addition of nickel–aluminum alloy to a reducible material dissolved in a suitable hydroxylic solvent leads to hydrogenation and/or hydrogenolysis of a wide variety of functional groups. Some multiple-bond types that can be saturated are indicated in Figure 1. In addition, nearly all N–N or N–O bonds can be cleaved at room temperature by using this reagent combination; functional groups that have been successfully reduced in this way are shown in Figure 2. Hydrogenolyses of bonds between carbon on the one hand and sulfur, halogen, oxygen, nitrogen, arsenic, mercury, and even carbon on the other can also be effected, as summarized in Figure 3. However, some functional groups such as the carboxylate anions, esters, and amides are never reduced (though hydrolysis of base-sensitive moieties is often observed).

TABLE I. Carbon–Carbon Multiple Bonds Reported To Be Saturated with Nickel–Aluminum Alloy[a]
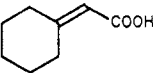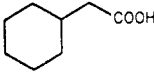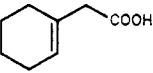
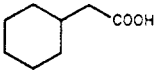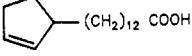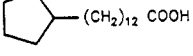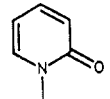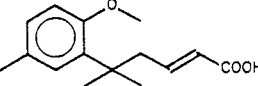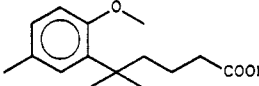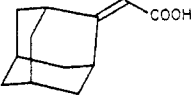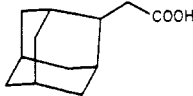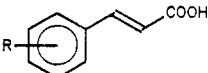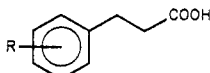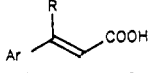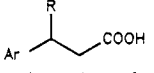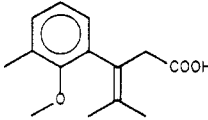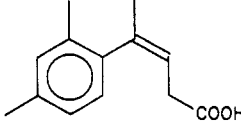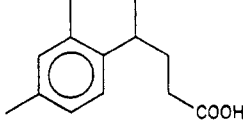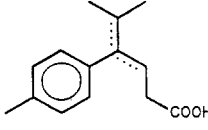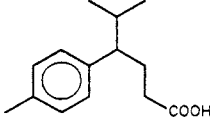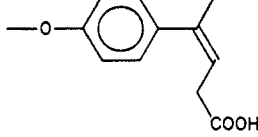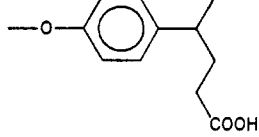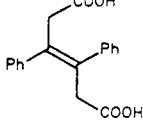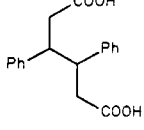| reaction no.	starting material	product(s)	yield, %	comments	ref
I-1*	$CH_3CH{=}CHCOOH$	$CH_3(CH_2)_2COOH$	80		24
I-2	cis-$HOOCCH{=}CHCOOH$	$HOOC(CH_2)_2COOH$	90		24
I-3	(cyclohexylidene–COOH)	(cyclohexyl–COOH)	80		24
I-4	(cyclohexenyl–CH₂COOH)	(cyclohexyl–CH₂COOH)	15		24
I-5	cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$CH_3(CH_2)_{16}COOH$	100		24
I-6	(cyclopentenyl–$(CH_2)_{12}$ COOH)	(cyclopentyl–$(CH_2)_{12}$ COOH)	100		24
I-7	(1-methyl-2-pyridone)	(1-methyl-2-piperidone)	90		20
I-8*	(aryl structure, COOH)	(aryl structure, COOH)	97		25
I-9	(adamantylidene–COOH)	(adamantyl–CH₂COOH)	98.5		26
I-10*	$PhCH{=}CHCOCH_3$	$PhCH_2CH_2COCH_3$	78		27
	(R–C₆H₄–CH=CH–COOH)	(R–C₆H₄–CH₂CH₂–COOH)			
I-11*	R = 3-OH	R = 3-OH	97		28
I-12*	R = H	R = H	95		24
I-13*	R = 4-OCH_3	R = 4-OCH_3	95		29
I-14*	R = 2-OCH_3	R = 2-OCH_3	94		30
I-15*	R = 2-COOH	R = 2-COOH	92–95		16
	(Ar–C(R)=CH–COOH)	(Ar–CH(R)–CH₂–COOH)			
I-16*	Ar = 2-methoxy-4-methylphenyl R = methyl	Ar = 2-methoxy-4-methylphenyl R = methyl	84		31
I-17*	Ar = 2-methoxy-5-methylphenyl R = methyl	Ar = 2-methoxy-5-methylphenyl R = methyl	78		32
I-18*	Ar = 2-methoxy-3-methylphenyl R = isopropyl	Ar = 2-methoxy-3-methylphenyl R = isopropyl	none given		33
I-19	(aryl structure, COOH)	no reaction			33
I-20*	(aryl structure, COOH)	(aryl structure, COOH)	82		34
I-21*	(aryl structure, COOH)	(aryl structure, COOH)	85		35
I-22*	(aryl ether structure, COOH)	(aryl ether structure, COOH)	62–70		36
I-23	(Ph,Ph diene diCOOH)	(Ph,Ph diCOOH)	84	racemic product	37

TABLE I (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
I-24			80–100	meso product	37
I-25			52	meso product	37
I-26		no reaction	–		37
I-27			90–95	Raney nickel hydrogenation leads to cyclooctane	38
I-28*			93		39
I-29*			90		39
I-30			85		30
I-31*	Ar = 4-hydroxyphenyl Ar′ = phenyl	Ar = 4-hydroxyphenyl Ar′ = phenyl	95		24
I-32*	Ar = 4-methoxyphenyl Ar′ = phenyl	Ar = 4-methoxyphenyl Ar′ = phenyl	90		24
I-33*	Ar = phenyl Ar′ = 4-methoxyphenyl	Ar = phenyl Ar′ = 4-methoxyphenyl	90		24
I-34*	Ar = phenyl Ar′ = 4-hydroxyphenyl	Ar = phenyl Ar′ = 4-hydroxyphenyl	95		24
I-35*			85		24
I-36*			80	diastereomer ratio in product was 50:30 (Raney nickel gave only one isomer)	24
I-37*			none given	racemate was isolated	40
I-38*			66.5		41
I-39*			69	23–26 °C	42
I-40*			80	temperature was raised from 50 to 95 °C during the reaction course	43
I-41*			20–25	at 20–30 °C	43
		+	65–70		

TABLE I (Continued)
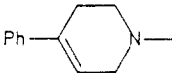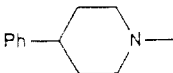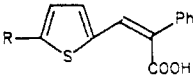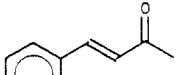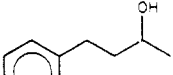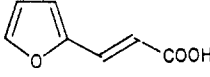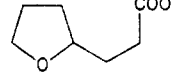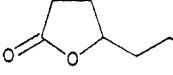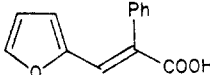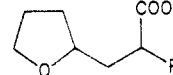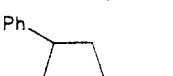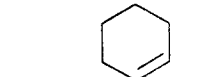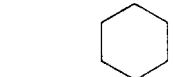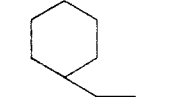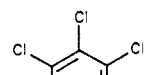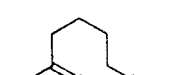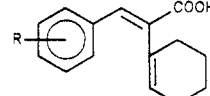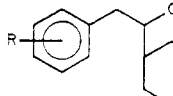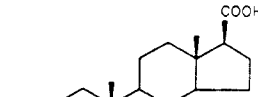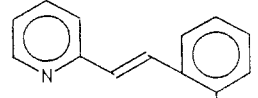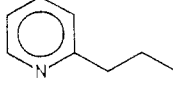
reaction no.	starting material	product(s)	yield, %	comments	ref
I-42		R(CH$_2$)$_5$CHPhCOOH	83		44
I-43*	R = Et	R = Et	none given		45
I-44*	R = CH$_2$Ph	R = CH$_2$Ph	74		46
I-45*	R = CH$_2$CH$_2$Ph	R = CH$_2$CH$_2$Ph	70		46
I-46*			85		47
I-47*		+	34–39 33–37		17
I-48*		+	31 55		48
I-49*		+	35 42		48
I-50*			none given		49
I-51*	PhCH=CHCOCH=CHPh	[PhCH=CHCOCH$_2$CHPh]$_2$	50		47
I-52	*trans,trans*-CH$_3$CH=CHCH=CHCOOH	CH$_3$(CH$_2$)$_4$COOH	80		24
I-53*	R = H	R = H	90		24
I-54*	R = 4-OH	R = 4-OH	90		24
I-55		no reaction			24
I-56	alkenes	no reaction		with Ni–Al in formic acid	50
I-57*			65		51

TABLE I (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
I-58*			74		51
I-59*			none given		52
I-60*			78		52
I-61	PhC≡CCOOH	PhCH₂CH₂COOH	80		24

_a For additional instances in which carbon–carbon multiple bonds are reduced, see also II-2, II-3, II-6, II-7, III-47, III-48, III-49, III-50, III-70, IV-9, VI-18, VI-20, VII-15, VIII-18, IX-18, IX-19, IX-20, IX-36, IX-38, IX-39, IX-40, IX-41, IX-56, X-3, and XV-35. For additional instances in which carbon–carbon multiple bonds survive reduction, see also II-8, II-31, II-81, and VI-20. An asterisk indicates that the stereochemistry of the material(s) encountered in this reaction was not specified in the original reference, so the single stereochemical representation given has been arbitrarily chosen.

pendence of olefin reactivity upon structure can be found in reactions I-18 and I-19, in which a mixture of two isomeric olefins was exposed to nickel–aluminum alloy in base. Only the α,β-unsaturated isomer (a trisubstituted olefin) (I-18) was hydrogenated while the tetrasubstituted β,γ-isomer (I-19) remained unreacted.

Only one attempt to reduce a triple bond (reaction I-61) has been reported in the literature thus far. The result, conversion of 3-phenylprop-2-ynoic acid to 3-phenylpropanoic acid in 80% yield, suggests that triple bonds as well as double bonds may be amenable to efficient reduction by nickel–aluminum alloy in base when the molecular structure is otherwise similar.

2. Aromatic Compounds

Carbocyclic and heterocyclic aryl rings also appear to be reducible with nickel–aluminum alloy, but more vigorous conditions are often required for reduction of aromatic compounds than of olefins. The reactions of a wide variety of aryl ring compounds with this reducing system have been studied,[19,20,27,48,53–59] as shown in Table II.

Reactions II-3 and II-4 illustrate the point that phenyl or substituted phenyl rings usually are refractory to reduction even when conversion of other functional groups in the same molecule is nearly complete. Nevertheless, simple phenyl groups can sometimes be hydrogenated in good yield, as reaction II-48 demonstrates.

Naphthalene rings, on the other hand, are usually reduced to the tetralin. Reaction II-1 and many others illustrate this point. The tricyclic aromatic compound phenanthrene is reduced to a mixture of di-, tetra-, and octahydro derivatives, as shown in reaction II-29.

Furans can be reduced to the corresponding tetrahydrofurans, as in example I-47. Overreduction to ring-opened products that then cyclize to lactones on workup has frequently been observed to accompany tetrahydrofuran formation (e.g., reaction I-47).

Thiophenes are easily reduced by nickel–aluminum alloy in base. Extrusion of sulfur accompanies saturation of the ring, making the 2-thienyl moiety the syn-

thetic equivalent of the n-butyl group under these conditions. We shall discuss hydrogenolytic removal of sulfur and other atoms from the carbon chain in more detail in section III.B.

Pyrrole proved more resistant to reduction by nickel–aluminum alloy in base, pyrrolidine being produced in only 58% yield after 4 days (reaction II-38). Pyrazoles (example II-36) and imidazole (II-37) were not reduced under these conditions. Oxazole (reaction II-43) and an isoxazole (example II-44) were reduced with ring-opening to form the corresponding 1,2- and 1,3-alkanolamines, respectively.

It has been reported that 6-nitroindoline was reduced to 6-aminoindole (II-33), a reaction that exhibits a concomitant nitro group reduction and heterocyclic ring oxidation. In our hands, replication of the conditions of reaction II-33 gave only a small quantity of unidentified oil, but reduction at room temperature yielded 6-aminoindoline in 52% yield.[23]

Pyridines in wide variety have recently been shown to be easily reduced in good yields to the corresponding piperidines, as illustrated in reaction II-50, despite an earlier indication[61] that pyridine showed no reaction other than hydrogen isotope exchange when exposed to nickel–aluminum alloy in base at 90 °C. Pyridine N-oxides can be deoxygenated to pyridines (reaction II-79), with further reduction to the piperidine (example II-67) also being frequently observed. Pyrazines are usually converted to piperazines (example II-70), but tetrasubstitution can leave the ring unreactive (reaction II-74). Pyrimidines (II-75) and pyridazines (example II-76) can be reductively ring-opened to the corresponding 1,3- or 1,4-diamines, respectively, in preparatively useful yields.

Further evidence that the stereochemistry of hydrogen addition is usually predominantly cis can be seen in Table II. For example, 2,6-dimethylpyridine gave cis-2,6-dimethylpiperidine as the major product (II-53).

3. Carbonyl Compounds

Aldehydes and ketones are nearly always easily reduced with nickel–aluminum alloy in alkaline medi-

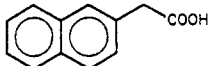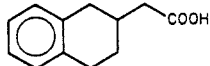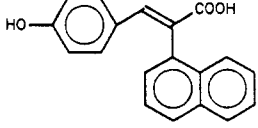**TABLE II. Aromatic Compounds Reported To Be Reduced with Nickel–Aluminum Alloy[a]**
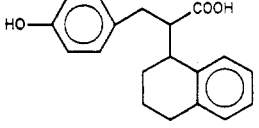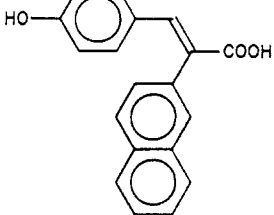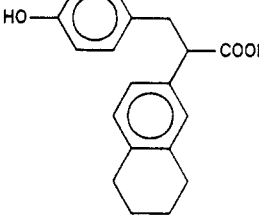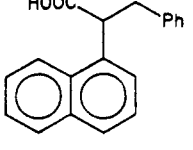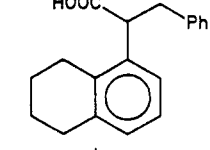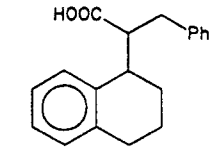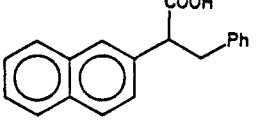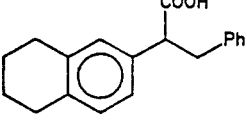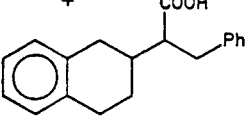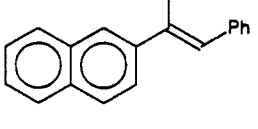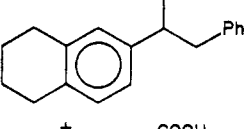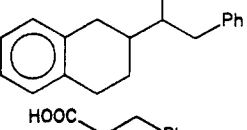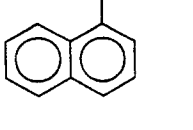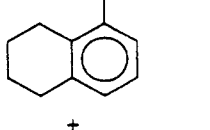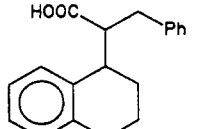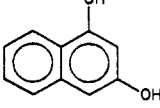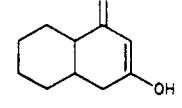
reaction no.	starting material	product(s)	yield, %	comments	ref
II-1			83		53
II-2*			98		53
II-3*			98		53
II-4			none given		53
II-5				individual yields were not calculable, but the product ratio was 5:2, respectively	53
II-6*			60		53
			10		
II-7*			25		53
			49		
II-8			none given	structural assignments tentative	53

TABLE II (Continued)
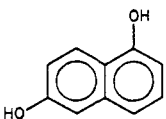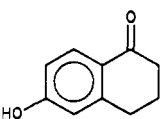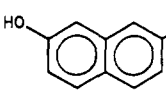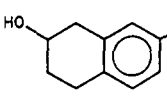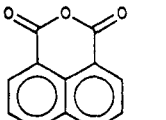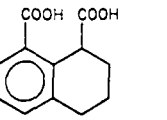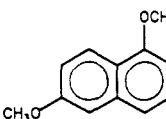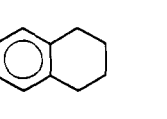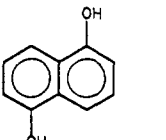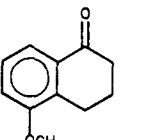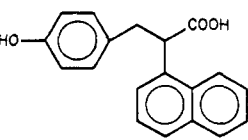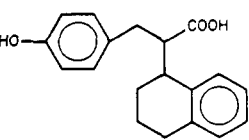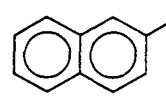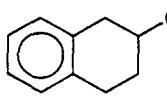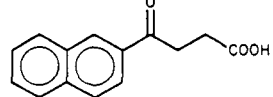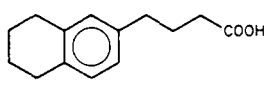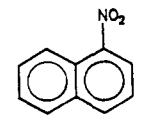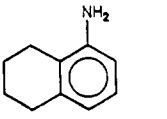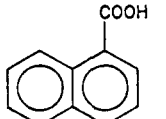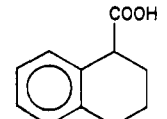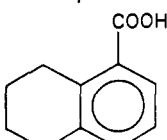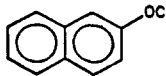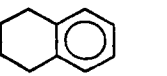
reaction no.	starting material	product(s)	yield, %	comments	ref
II-9			60	product could not be further reduced	53
II-10			86		53
II-11			86		53
II-12			none given	other products were also detected	53
II-13			19	analyzed after methylation with dimethyl sulfate	53
II-14*			85		53
II-15	R = H	R = H	74		53
II-16	R = 1-CH$_2$COOH	R = 1-CH$_2$COOH	70		53
II-17	R = 2-COOH-3-OH	R = 2-COOH-3-OH	85		53
II-18	R = 1-OH-2-COOH	R = 1-OH-2-COOH	80		53
II-19	R = 2-COOH	R = 2-COOH	85		53
II-20	R = 1-OH	R = 1-OH	85		53
II-21			68		53
II-22			58		53
II-23			65		53
II-24			78	yield given is total yield; isomers could not be separated	53
II-25			20		53

TABLE II (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
II-26	R = 1-CN, 2-CN, 1-NO$_2$	naphthyl ring does not react with nickel–aluminum alloy in formic acid			50
II-27			3.8	plus other products shown in reaction III-9	19
		+	5		
II-28			87		27
II-29			none given		23
		+	none given		
		+	none given		
		+	none given		
II-30			30		54
II-31			68.7	the 2-methyl homologue was also reduced, giving a mixture of products	55
II-32*			none given	structure is tentative	56
II-33			43		57

TABLE II (Continued)
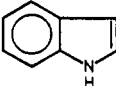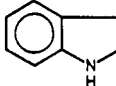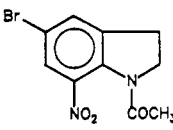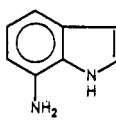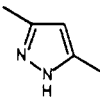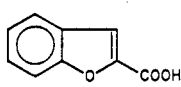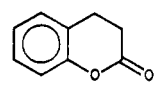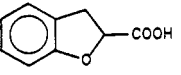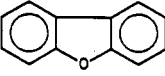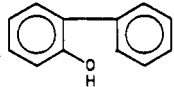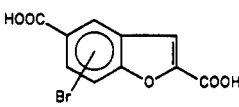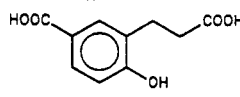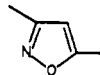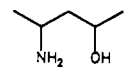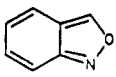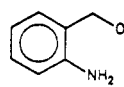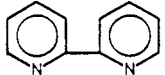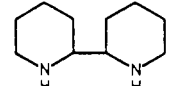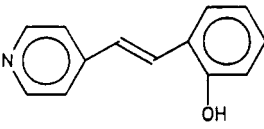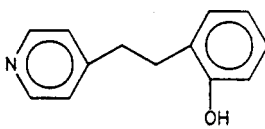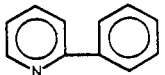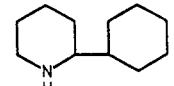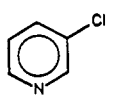
reaction no.	starting material	product(s)	yield, %	comments	ref
II-34			73		58
II-35			49		57
II-36		no reaction			58
II-37		no reaction			58
II-38			none given	only partial (58%) reduction observed after 4 days	58
II-39			72		48
II-40		no reaction			48
II-41			low	product identification is tentative	48
II-42			60	product identification is tentative	48
II-43		$HOCH_2CH_2NHCH_3$	28		58
II-44			75		58
II-45			65		58
II-46			83		20
II-47*			74	no reduction of pyridine ring occurred	51
II-48			63		20
II-49			58		20
II-50	R = H	R = H	74		20
II-51	R = 2-Me	R = 2-Me	77		20
II-52	R = 2-Et	R = 2-Et	79		20
II-53	R = 2,6-Me$_2$	R = 2,6-Me$_2$	53	product has mostly cis stereochemistry	20
II-54	R = 2-CONHMe	R = 2-CONHMe	61		23

TABLE II (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
II-55	R = 3-CONHMe	R = 3-CONHMe	56		20
II-56	R = 4-CONHMe	R = 4-CONHMe	72		20
II-57	R = 4-CONHEt	R = 4-CONHEt	79		20
II-58	R = 4-CONHPh	R = 4-CONHPh	57		20
II-59	R = 3-CONEt$_2$	R = 3-CONEt$_2$	75		20
II-60	R = 3-Me	R = 3-Me		only 27% reduction after 168 h	20
II-61	R = 4-Me	R = 4-Me		only 13% reduction after 168 h	20
II-62	R = H	R = H	84		20
II-63	R = Me	R = Me	89		20
II-64			74		20
II-65			none given	the ring-reduced hydrazide was seen as an intermediate	20
II-66			49		20
II-67			59		20
II-68			76		58
II-69			68		58
II-70			70		58
II-71			76		58
II-72			76		58
II-73			74		58
II-74		no reaction			58
II-75			69		58
II-76			61		58
II-77			56		58
II-78			53		58
II-79			none given		20

TABLE II (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
II-80			90		59
II-81			34		59
		+	16		
II-82			20		59
II-83		no reaction		no reaction with nickel–aluminum alloy in formic acid	50

[a] For additional instances in which aromatic compounds are reduced, see also III-17, X-4, and XIV-11. For further examples of hetero-aromatic reduction, see also I-43, I-44, I-45, I-47, I-48, and I-49. Many other instances of thiophene reduction are listed in Tables IX and XV. For additional instances in which heteroaromatic compounds are not reduced, see also I-57, I-58, V-11, VI-10, and XV-20. An asterisk indicates that the stereochemical representation drawn may not accurately reflect that of the material(s) used.

um.[19,27,29,43,47,62-72] Numerous examples illustrating this point are summarized in Table III. The carbonyl group may remain unreacted under certain conditions, however. For example, the starting p,p'-dimethoxybenzil of reaction III-33 was reduced in 80% yield to the diol when both ethanol and toluene were mixed with the aqueous reaction mixture, but the corresponding benzoin was isolated in 80% yield when the ethanol was omitted. Normally, however, facile reduction of ketones and aldehydes in preparatively significant yields is observed under these conditions.

The carbonyl groups of carboxylic acids and their amides and esters, on the other hand, are never reduced by nickel–aluminum alloy in base. A case in point is the β-keto carboxamide of reaction III-41, which was converted to the β-hydroxy amide in 60% yield. Of course, reaction conditions may induce nonredox changes in the carboxylate function, including hydrolysis or formation of ester linkages, as in examples I-28 and III-53, respectively.

Even thioesters do not suffer carbonyl reduction in the presence of nickel–aluminum alloy. The sulfur atom is hydrogenolyzed, as illustrated in reaction III-34, but the carbonyl group remains in the carboxylate oxidation state.

The stereochemistry of reduction is normally expected to be cis. In a series of cyclic α,β-unsaturated ketones, for example, Hayes observed 80–96% yields of the products in which all hydrogens were added from the same side of the molecule (e.g., see reaction III-47). Exceptions to this generalization may be encountered, however. For instance, anthraquinone was reportedly converted to the trans- rather than the cis-dihydrodiol

(reaction III-19). We speculate that this difference from the outcome normally expected in a catalytic hydrogenation results from the influence of the dissolving-metal component of reductions with nickel–aluminum alloy in base; however, normal catalytic reduction of the two carbonyls during separate encounters of the nickel surface with opposite faces of the molecule would give the same stereochemical result and can certainly not be excluded.

In contrast to the unexceptional conversion to the alcohol resulting from reduction of most aldehydes and ketones, carbonyl groups directly attached to an aromatic ring may be subject to four- as well as two-electron reduction. Salicylaldehyde, for example, is reduced to o-hydroxybenzyl alcohol at temperatures of 10–20 °C (reaction III-61), but to o-cresol at 90 °C (III-62). This overreduction presumably reflects the propensity of the initially produced benzyl alcohols to undergo hydrogenolysis of the C–O bond and will thus be considered in greater detail in section III.B.1.
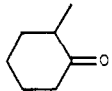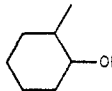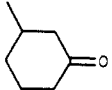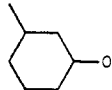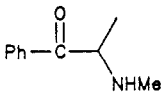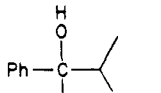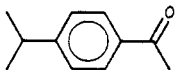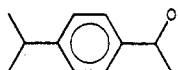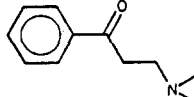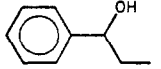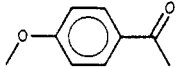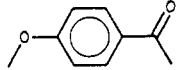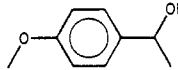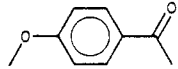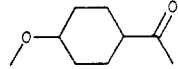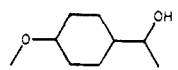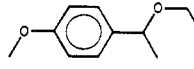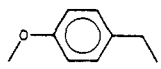
4. Nitriles

Cyano groups are reduced by nickel–aluminum alloy with exceptional ease,[18,50,67,74] but very different products are observed under basic versus acidic conditions, as summarized in Table IV.

In aqueous alkali, facile four-electron reduction to the corresponding primary amine was the result of every application found in the literature, as shown in the first ten entries of Table IV.

In aqueous formic acid solution, on the other hand, two-electron reduction accompanied by hydrolysis al-

TABLE III. Reduction of Carbonyl Groups Using Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
	CH₃COR	CH₃CHOHR			
III-1	R = n-propyl	R = n-propyl	54		27
III-2	R = isopropyl	R = isopropyl	68		27
III-3			67		27
III-4			80	stereochemistry was unspecified	47
			none given	product was 90% trans/10% cis; best yields were with Me₃N as base	62
III-5			none given	75% cis/25% trans (stereoselectivity was like that of metal hydrides, opposite that of preformed nickel/H₂)	62
III-6			none given	74% trans/26% cis	62
	RCOCH₂R′	RCHOHCH₂R′			
III-7	R = PhCH₂, R′ = H	R = PhCH₂, R′ = H	74		27
III-8	R = PhCH₂, R′ = Ph	R = PhCH₂, R′ = Ph	70		47
III-9	R = Ph, R′ = H	R = Ph, R′ = H	75		27
			81–92	plus other products shown in reaction II-27	19
			66	in neutral aqueous solution at 50–60 °C	19
III-10	R = Ph, R′ = Me	R = Ph, R′ = Me	81		19
III-11	R = Ph, R′ = Et	R = Ph, R′ = Et	42–76	inverse addition gave the larger yield	19
III-12*			low		19
III-13			75.6	plus 21.9% starting material	19
III-14			100		19
III-15	PhCOPh	PhCHOHPh	76.7	plus 19.5% starting material	19
III-16			50		29
III-17			57.2		19
		+	38.2		
		+	—		
		+	—	these products were identified in small amounts at higher reaction temperature	
		+	—		
		+	—		

TABLE III (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
III-18			60–100	some β-estradiol was also produced	63, 64
III-19			16		19
III-20			70		47
III-21	R = CH₃	R = CH₃	72		47
III-22	R = CH₃CH₂	R = CH₃CH₂	78		47
III-23	R = Ph	R = Ph	90		47
III-24	PhCOCH₂Ph	PhCH₂CH₂Ph	70		47
III-25	PhCO(CH₂)₈COOH	Ph(CH₂)₉COOH	~50		65
III-26			none given		65
III-27			85		65
III-28			76		47
III-29			70		29
III-30			67		29
III-31			65		29
III-32	PhCOCOPh	PhCOCHOHPh	40	almost no benzilic acid was produced	19
III-33*			80	with toluene present	47
		or			
			80	with both toluene and ethanol present	47
III-34			54		66
III-35	PhCHOHCOPh	PhCHOHCHOHPh	30	product had meso stereochemistry	19
		or PhCH₂CH₂Ph	50		47

TABLE III (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
III-36	RCOR′	no reaction with nickel–aluminum alloy in formic acid			50
	R–C(=O)–CH₂CH₂–COOH	(γ-butyrolactone R-substituted)			
III-37	R = Me	R = Me	53–65	plus Me(CHOH)(CH₂)₂COOH	27
III-38	R = Ph	R = Ph	none given		19
III-39			80	with cooling	27
		or			
			80	with heating	27
III-40			70		29
	RCOCH₂CONHR′	RCHOHCH₂CONHR′			
III-41	R = methyl R′ = phenyl	R = methyl R′ = phenyl	60		67
III-42	R = methyl R′ = o-tolyl	R = methyl R′ = o-tolyl	60–70		67
III-43	R = phenyl R′ = phenyl	R = phenyl R′ = phenyl	60–70		67
III-44			87	with ethanol added	27
			60.5		19
III-45			15		47
III-46			100		19
III-47			95	Li/NH₃ gives the configuration in which the OH is on the same side of the molecule as the hydrogens	68
III-48			96		68
III-49			80		68
III-50			90		68
III-51			68		66

TABLE III (Continued)
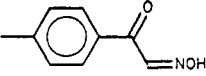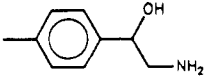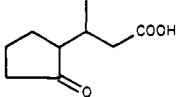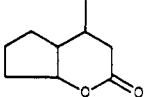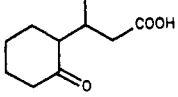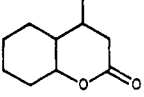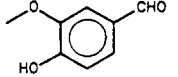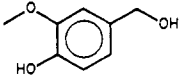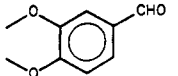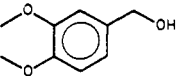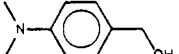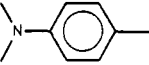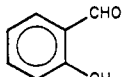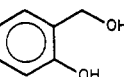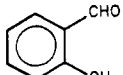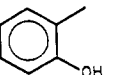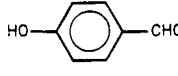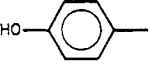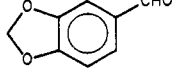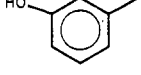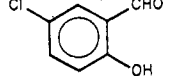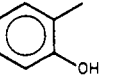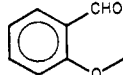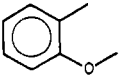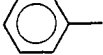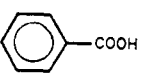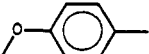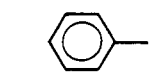
reaction no.	starting material	product(s)	yield, %	comments	ref
III-52			none given		69
III-53			99	lactonization occurred on acidifying the hydroxy acid	70
III-54			91		70
III-55	$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_6OH$	57		27
III-56			85		27
III-57			66		27
III-58			70	a small amount of *N,N*-dimethyl-*p*-toluidine was also detected	27
		or			
			70		29
III-59	PhCHO	$PhCH_2OH$ + $PhCH_3$	none given		19
III-60	PhCHO	$PhCH_3$	60		47
III-61			77	10–20 °C	27
III-62			75–76	90 °C	27, 47
III-63			80		47
III-64			60		43
III-65			75		29
III-66			45		29
		+			
			15		
		+			
			20		
III-67			30		29
		+			
			45		

TABLE III (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
III-68	(ethoxy-benzaldehyde structure)	(benzoic acid structure) —COOH	40		29
		+ (ethoxy-toluene structure)	15		
		+ (toluene structure)	25		
III-69	(methoxy-benzaldehyde structure)	(methoxy-xylene structure)	55		29
III-70*	PhCH=CHCHO	Ph(CH₂)₃OH	50		47
III-71	(sugar structure)	(sugar alcohol structure)	80–85		71, 72

Note: III-70 Ph(CH₂)₃OH should be $Ph(CH_2)_3OH$; III-68 starting material shows an ethoxy group, product —COOH.

^{a} For instances in which carbonyls are reduced, see also I-46, II-22, II-27, II-28, V-26, VI-12, VI-17, VI-19, VI-20, VIII-8, VIII-19, IX-36, IX-39, IX-40, IX-41, IX-44, IX-45, IX-46, IX-48, XII-21, and XIV-20. For instances in which carbonyls are not reduced, see also I-10, I-51, II-8, II-9, II-13, II-31, VI-20, VII-6, VII-7, IX-21, IX-22, IX-23, IX-24, IX-25, IX-33, IX-34, IX-35, IX-36, IX-38, IX-39, IX-40, IX-45, and XII-21. An asterisk indicates that the stereochemistry in the indicated structures is arbitrarily assigned, as configuration is not specified in the original references.

ways led to the aldehyde, which was not further reduced. Examples of this interesting variation are found in entries IV-11 through IV-27 of Table IV. Yields of aldehyde are normally quite good for aryl nitriles, but lower (12–40%) when the product is capable of aldol condensation (as in reaction IV-24, for example). Selectivity in this system is quite different from that in aqueous alkali. The aldehyde functional group of the product is not the only one that remains unreduced in formic acid; olefins (example IV-22), halides (IV-18), and sulfur-containing substituents (IV-19) can survive nitrile reduction unscathed as well.

5. Oximes and Hydrazones

Like the nitriles, oximes generally undergo uncomplicated reduction to primary amines in alkaline media.[27,67,69,75–79] Examples of this conversion are listed in Table V (e.g., reaction V-7). Skeletal rearrangement of the type sometimes observed with other reductants such as the complex metal hydrides appears never to occur with nickel–aluminum alloy, an advantage that will be discussed in more detail in section VI.

Hydrazones contrast with the oximes somewhat in that, although the primary amine is the expected product[41,69,80] in both cases, additional products are often reported in reductions of hydrazones. Several examples of this are found in Table VI. Reaction VI-1 shows that reduction of a hydrazone with another functional group capable of participation in a reductive amination reaction elsewhere in the molecule can give rise to considerable secondary as well as primary amine formation, although it is not clear what the mechanism of the reaction is. Overreduction of the hydrazone function to the corresponding –CH₂– derivative can also take place, as illustrated in reaction VI-6. An example of a carbon–carbon bond cleavage under these conditions has even been reported, as shown in reaction VI-19, though the apparent structural change involved

is so difficult to explain that the reaction should probably be reinvestigated before final conclusions are made.
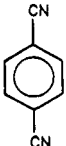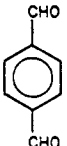
We believe that the more complicated course of hydrazone versus oxime reduction can be rationalized in terms of the former functional group's greater ease of hydrolysis to the corresponding carbonyl compound in basic medium. Reduction of only one hydrazone group in the starting material of reaction VI-1, with concomitant hydrolysis of the other hydrazone function, would produce a γ-amino ketone capable of cyclization to the observed pyrrolidine under reducing conditions. Support for this interpretation is found in the work of Tyman, who reported that aldehydes and ketones could be reductively aminated when nickel–aluminum alloy was added to the carbonyl compound in aqueous ammonia solution.[19] In addition, a bishydrazone was reduced to the corresponding alkanolamine (reaction VI-15), indicating hydrolysis of one of the C=N bonds prior to reduction. The reduction of hydrazones to hydrocarbons (as in isolation of ethylbenzene from reaction VI-6), which is superficially similar to the Clemmensen and Wolff–Kishner reductions, could occur if hydrolysis to the ketone took place before the C=N double bond was saturated. The resulting aryl ketone is capable of conversion to the benzylic alcohol which, as described in section III.A.3, can be further reduced to the hydrocarbon. Hydrogenolysis of benzylic C–O bonds will be further discussed in the next section.

B. Hydrogenolysis Reactions

1. Cleavage of Carbon–Oxygen Bonds

Ethers and alcohols are normally inert to reduction with nickel–aluminum alloy. However, there are certain structural features that predispose the carbon–oxygen bond to facile cleavage,[17,29,37,43,47,48,53,58,66,71,72,76,81–84] and by now numerous examples have been reported, as summarized in Table VII. Several categories of re-

TABLE IV. Reduction of Nitriles with Nickel–Aluminum Alloy in Base versus Acid[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
		Reductions in Aqueous Alkali			
	RC≡N	RCH₂NH₂			
IV-1	R = phenyl	R = phenyl	39	plus 2% dibenzylamine	74
			62		67
IV-2	R = benzyl	R = benzyl	52		74
			76		67
IV-3	R = 3,4-dimethoxybenzyl	R = 3,4-dimethoxybenzyl	41		74
IV-4	R = 2-methoxyphenyl	R = 2-methoxyphenyl	31		74
IV-5	R = 4-methoxyphenyl	R = 4-methoxyphenyl	16		74
			79		67
IV-6	R = 4-ethoxyphenyl	R = 4-ethoxyphenyl	16		74
IV-7	R = 1-naphthyl	R = 1-naphthyl	82		67
IV-8	R = n-pentyl	R = n-pentyl	52		67
IV-9*	PhCH=CHCN	Ph(CH₂)₃NH₂	36		67
IV-10	NCCH₂CH₂CN	H₂N(CH₂)₄NH₂	9		67
		Reductions in Aqueous Formic Acid			
	RC≡N	RCHO			
IV-11	R = phenyl	R = phenyl	97		18, 50
IV-12	R = 2-methylphenyl	R = 2-methylphenyl	70		50
IV-13	R = 3-methylphenyl	R = 3-methylphenyl	90		50
IV-14	R = 4-methylphenyl	R = 4-methylphenyl	93		50
IV-15	R = 2-hydroxyphenyl	R = 2-hydroxyphenyl	95		50
IV-16	R = 4-methoxyphenyl	R = 4-methoxyphenyl	93		18, 50
IV-17	R = 2-chlorophenyl	R = 2-chlorophenyl	73		50
IV-18	R = 4-chlorophenyl	R = 4-chlorophenyl	100		18, 50
IV-19	R = 4-sulfonamidophenyl	R = 4-sulfonamidophenyl	63–70		18, 50
IV-20	R = 1-naphthyl	R = 1-naphthyl	65–70		50
IV-21	R = 2-naphthyl	R = 2-naphthyl	95		18, 50
IV-22*	R = 2-phenylvinyl	R = 2-phenylvinyl	70		50
IV-23	R = 3-pyridyl	R = 3-pyridyl	37		50
IV-24	R = methyl	R = methyl	12		50
IV-25	R = n-pentyl	R = n-pentyl	40		50
IV-26	R = n-hexyl	R = n-hexyl	28		50
IV-27			70		50

[a] For the reduction of nitriles with nickel–aluminum alloy in base, see also XV-46. For instances of reduction of nitriles with nickel–aluminum alloy in acid, see also X-20 and X-21. An asterisk indicates that the stereochemistry in the structure shown is arbitrarily assigned, as configuration is not specified in original reference.

active structure appear to be emerging from the data at hand.

One includes the benzylic compounds mentioned in section III.A. Thus benzyl alcohol is converted to toluene (reaction VII-1) and benzyl ethers can be debenzylated in high yield (example VII-5). In addition, aryl ketones can often be reduced to the corresponding ArCH₂ derivatives, presumably by hydrogenolysis of the benzylic alcohol produced on reduction of the carbonyl group. An example of such carbonyl-to-hydrocarbon conversion is found in reaction III-66, in which o-methoxytoluene is observed as the major product of o-methoxybenzaldehyde reduction.

Aryl ethers can also be reduced, often in excellent yield, with the ether substituent normally being replaced by hydrogen on the aromatic ring. This outcome seems to be particularly favorable when the ether oxygen is ortho or para to a suitably activating substituent. Some typical examples of this phenomenon are the quantitative conversion of p-anisic acid to benzoate (reaction VII-13) and the opening of the methylenedioxy ring of veratric acid to give m-hydroxybenzoate in 80% yield (reaction VII-20). Aryl–oxygen cleavage at the activated carbon para to the carbonyl group presumably initiates the reaction, with alkyl–oxygen

cleavage of the resulting formaldehyde hemiacetal being hydrolytic rather than reductive. While aryl–oxygen cleavage appears to be the normal expectation, however, reductive alkyl–oxygen rupture is possible; this point is illustrated in reaction VII-14, in which an α-phenoxy-β-arylpropionic acid was cleaved to phenol and the α-unsubstituted aryl propionate, albeit in low yield. Alkyl–oxygen cleavage may have predominated in the latter case because there were no activating substituents on the phenyl ring to labilize the quaternary aryl carbon toward reductive attack, making the aryl–oxygen bond unreactive. Support for this view can be found in the experience with certain other phenoxy compounds. For example, diphenyl ether gave no reaction on treatment with nickel–aluminum alloy in base (reaction VII-26). On the other hand, reduction of unsubstituted phenoxy compounds to benzene can sometimes be observed, as demonstrated in reaction VII-16.

Aryl sulfate esters can undergo a similar reductive cleavage of the aryl–oxygen bond. As shown in example VII-22, the bis-sulfate ester of anthracene-9,10-diol is converted to anthracene after dehydrogenation of the ring-reduced intermediate. While the yield of this reaction was not stated, a similar transformation (reaction VII-23) proceeded in a yield of 80%, suggesting prep-

arative significance. It is not clear whether displacement of the sulfate occurs directly on the aromatic ring or by some alternative, indirect mechanism; it is easy to visualize these anthracene derivatives as being reduced initially to the 9,10-dihydrodiol (after initial hydrolytic loss of the sulfate group) and/or esters thereof, following which deoxygenation could occur by reductive cleavage of the resulting benzylic carbon–oxygen bond as discussed earlier in this section.

It seems likely that many other types of neighboring group facilitation of carbon–oxygen cleavage may be possible. A final example that can be cited from the data at hand is that of the α-methoxy nitrosamines. Reaction VII-8 shows that both the methoxy and the N-nitroso groups of N-nitrosomethyl(1-methoxyethyl)amine are reductively removed, leading to methylethylamine in 89% yield.

2. Quantitative Halide Removal

A common effect of treating an organic compound with nickel–aluminum alloy in basic medium is the replacement of all halogen atoms by hydrogen.[19,23,29,49,60,85–96] As shown in Table VIII, a great many chlorides and bromides have been successfully subjected to this transformation. Even fluorine can be cleaved in preparatively significant yield, as shown in example VIII-34. While little work has been attempted with iodides, they would be expected to be at least as susceptible to reductive cleavage as the other halides, and some data supporting this point exist (reaction VIII-20). The reaction is so facile that Papa, Schwenk, and co-workers proposed it as a quantitative analytical method for halogen in organic molecules.[60] Reduction fails, however, when attempted in formic acid rather than aqueous alkali-metal hydroxide, as shown in reaction VIII-32. This allows for selective reduction of certain substances with retention of the halide; for example, the p-chlorobenzonitrile in reaction IV-18 was quantitatively reduced to p-chlorobenzaldehyde.

A particular advantage of halide removal by this means is that it affords a most convenient route for selectively introducing hydrogen isotopes when the reaction is conducted in deuterium oxide or tritiated water. Many examples of this phenomenon will be cited in section IV.

3. Extrusion of Sulfur Atoms

One of the most dependable results of exposing organic compounds to nickel–aluminum alloy in base is the quantitative replacement of all sulfur atoms present by hydrogen,[29,45,46,55,56,66,97–107] as illustrated in Table IX. We have found only a few reports of the isolation of a sulfur-containing organic compound after exposure to nickel–aluminum alloy in base. For example, reaction IX-33 was found to allow 19% of the starting material, 2-(mercaptomethyl)-9,10-anthraquinone, to be reisolated as the corresponding thioether after treatment with limited quantities of reductant. When this same thioether was exposed to additional nickel–aluminum alloy, however, the only compounds identified in the completed reaction mixture were sulfur-free (reaction IX-34).

Not only mercaptans and thioethers, as mentioned in the previous paragraph, but also sulfonic acids (example IX-54), thioesters (reaction IX-41), disulfides

(IX-35), and sulfate esters (VII-22) have been successfully reduced with this reagent combination. Thienyl rings are reduced to the saturated four-carbon chain, as mentioned in section III.A.2. A selenide has even been converted (reaction IX-57) to a hydrocarbon devoid of heteroatoms by distillation from zinc and nickel–aluminum alloy.[108]

We conclude that extrusion of sulfur is a completely general result when adequate amounts of alloy are used in basic medium, as would be expected for a reduction involving considerable Raney nickel character. Some of these reactions were included in a 1958 review.[8]

Exposure to nickel–aluminum alloy in formic acid solution appears not to have any effect on sulfur-containing compounds, however, While this type of reaction has as yet been seldom attempted, at least one relevant study has been reported. As shown in example IX-55, an arenesulfonamide grouping was inert to treatment with the alloy in formic acid. It remains to be seen whether this unreactivity is a general characteristic of nickel–aluminum alloy in acid.

Nickel–aluminum alloy reduction has been proposed[109] as a procedure for removing thiophenols from phenols. These mixtures are obtained when hydrocarbon oils are purified, and the method allows the recovery of pure phenols.

As with the halides, sulfur removal provides a convenient method for introducing hydrogen isotopes into organic molecules. It is necessary only to conduct the reduction in basic deuterium oxide or tritiated water. More will be said about the applications of this simple procedure in section IV.
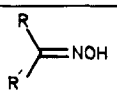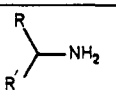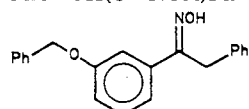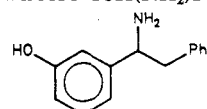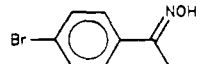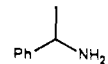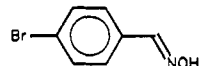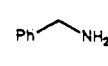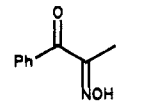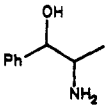
4. Reductive Cleavage of Nitrogen–Nitrogen and Nitrogen–Oxygen Bonds

Reduction of oximes and hydrazones was considered under III.A ("Hydrogenations") because saturation of the C=N bond is a general outcome, but this is not the only effect of nickel–aluminum alloy on these functional groups. Inspection of Tables V and VI reveals that the nitrogen–nitrogen and nitrogen–oxygen bonds are normally hydrogenolyzed as well. Together with findings for a wide variety of other compounds containing the N–N and/or N–O linkages, these data indicate that hydrogenolysis of such interheteroatom bonds is a fairly general result of treatment with nickel–aluminum alloy (Figure 2).[20,23,29,50,52,53,69,110–120]

As illustrated in Table X, for instance, C-nitro and -nitroso compounds undergo reduction to the corresponding amines, usually in preparatively significant yield. The course of reduction in basic medium is similar to that in aqueous formic acid, although the N-formyl derivative is usually the major product in the latter solvent. Interestingly, no amide production is observed in aqueous acetic acid, which led to the primary amine as the sole product observed. The differences among these three sets of reaction conditions are evident from a comparison of reactions VIII-53, X-11, and X-26. The starting p-halonitrobenzene is reduced to aniline in aqueous alkali, to p-haloformanilide in formic acid, and to p-haloaniline in acetic acid, respectively. Reaction X-1 demonstrates that a nitrosoarene can also be reduced to the corresponding aniline with nickel–aluminum alloy in base.

N-Nitro and -nitroso compounds also undergo facile reduction with this reagent combination. Some typical

TABLE V. Oxime Reduction Using Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
	R $\backslash$ C=NOH / R'	R $\backslash$ CH–NH₂ / R'			
V-1	R = H R' = phenyl	R = H R' = phenyl	50 60		67 75
V-2	R = H R' = 3,4-dimethoxyphenyl	R = H R' = 3,4-dimethoxyphenyl	51		75
V-3	R = H R' = 3,4-(methylenedioxy)phenyl	R = H R' = 3,4-(methylenedioxy)phenyl	48		75
V-4	R = H R' = 4-methoxyphenyl	R = H R' = 4-methoxyphenyl	63		67
V-5	R = H R' = hexyl	R = H R' = hexyl	67		67
V-6	R = H R' = 3-hydroxyphenyl	R = H R' = 3-hydroxyphenyl	none given		76
V-7	R = H R' = 3,5-dihydroxyphenyl	R = H R' = 3,5-dihydroxyphenyl	80		76
V-8	R = methyl R' = methyl	R = methyl R' = methyl	44		67
V-9	R = methyl R' = (1-methyl-3-piperidyl)methyl	R = methyl R' = (1-methyl-3-piperidyl)methyl	68	some alcohol formed	79
V-10	R = methyl R' = 3-hydroxyphenyl	R = methyl R' = 3-hydroxyphenyl	55		76
V-11	R = phenyl R' = 4-(4-pyrazolyl)butyl	R = phenyl R' = 4-(4-pyrazolyl)butyl	27		77
V-12	R = phenyl R' = cyclobutyl	R = phenyl R' = cyclobutyl	57		78
V-13	R = phenyl R' = phenyl	R = phenyl R' = phenyl	50 89		75 67
V-14	R = phenyl R' = methyl	R = phenyl R' = methyl	88 48		67 75
V-15	R = phenyl R' = ethyl	R = phenyl R' = ethyl	92		67
V-16	R = benzyl R' = benzyl	R = benzyl R' = benzyl	93 36		67 75
V-17	R = benzyl R' = 3,5-dimethoxyphenyl	R = benzyl R' = 3,5-dimethoxyphenyl	62		76
V-18	R = benzyl R' = 3-methoxyphenyl	R = benzyl R' = 3-methoxyphenyl	79		76
V-19	R,R' = -(CH₂)₄-	R,R' = -(CH₂)₄-	82		67
V-20	R,R' = -(CH₂)₅-	R,R' = -(CH₂)₅-	88 49		67 75
V-21	CH₃(C=NOH)₂CH₃	CH₃CH(NH₂)CH(NH₂)CH₃	8		67
V-22	PhCHOH(C=NOH)Ph	PhCHOHCH(NH₂)Ph	85		69
V-23			63		76
V-24			77		67
V-25			62		67
V-26			57–80		27, 69
V-27	R(C=NOH)R'	R(C=O)R'		oximes are hydrolyzed by nickel–aluminum alloy in formic acid	50

[a] For another example of oxime reduction, see also III-52.

results are summarized in Table XI. Diisopropyl-nitramine, for example, is converted to the corresponding secondary amine in 100% yield by exposure to nickel–aluminum alloy in base (reaction XI-20). Dimethylnitrosamine can be cleaved essentially quantitatively to dimethylamine, which can be isolated as the hydrochloride (reaction XI-1). N-Nitrosomethylaniline is reduced exclusively to N-methylaniline, with the absence of Fischer–Hepp rearrangement products being attributable presumably to the basic conditions employed (reaction XI-8). α-Nitrosamino ethers are reduced with concurrent cleavage of the N–N and C–O bonds, as mentioned in section III.B.1, but the result is not always as straightforward as the example cited there (VII-8); while dialkylamine was produced in 86–89% yield in reactions XI-12 and XI-13, the primary

TABLE VI. Hydrazones Reduced with Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
VI-1*			65		41
		+			
			29		
VI-2	R = H R′ = 2-methylpropyl	R = H R′ = 2-methylpropyl	69		41
VI-3	R = methyl R′ = methyl	R = methyl R′ = methyl	65		41
VI-4	R = H R′ = phenyl	R = H R′ = phenyl	14	some toluene was also isolated	41
VI-5	R = methyl R′ = hexyl	R = methyl R′ = hexyl	82		41
VI-6	R = methyl R′ = phenyl	R = methyl R′ = phenyl	25	some ethylbenzene was also isolated	41
VI-7	R = phenyl R′ = ethyl	R = phenyl R′ = ethyl	<5	some n-propylbenzene was also isolated	41
VI-8	R = benzyl R′ = methyl	R = benzyl R′ = methyl	71		41
VI-9	R = 4-methoxybenzyl R′ = methyl	R = 4-methoxybenzyl R′ = methyl	60		41
VI-10	R = H R′ = 2-furyl	R = H R′ = 2-furyl	72		41
VI-11			85–90		41
VI-12*	PhCOCH=NNHPh	PhCHOHCH$_2$NH$_2$	none given		69
		H$_2$NCHRCHR′NH$_2$			
VI-13*	R = H R′ = phenyl	R = H R′ = phenyl	none given		69
VI-14*	R = methyl R′ = methyl	R = methyl R′ = methyl	none given		69
VI-15*			none given		69
VI-16*			none given		69
VI-17*			none given		80
VI-18*			67		41
VI-19			none given	plus other products	80

TABLE VI (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
VI-20*	Ph—N≡N ... Ph ... OH	H₂N ... Ph ... OH	none given	in 2 h of reaction	80
		or			
		OH ... H₂N ... Ph ... OH	none given	in 8 h of reaction	80

[a] For another example of hydrazone reduction, see also I-38. As asterisk indicates that the actual stereochemistry of the indicated materials is unclear from the original literature; structures shown are arbitrarily chosen.

and secondary amines were produced in roughly equal amounts in reaction XI-11. Reduction of an O-alkyl-N-nitrosohydroxylamine led exclusively to the primary amine in reaction XI-10. The reduction of nitrosamines to the corresponding amines with nickel–aluminum alloy followed by the preparation of fluorescent derivatives of these amines has been proposed[115] as a means of determining nitrosamines. Interestingly, inorganic nitrate has been reduced to ammonia.[116]

Hydrazines have sometimes been observed as intermediates in the reduction of nitramines and nitrosamines[110,113] to amines, but their absence from the completed reaction mixture indicated that they are also cleaved quantitatively by nickel–aluminum alloy in base. This has proven to be a general reaction, as demonstrated in the data of Table XII. Thus, the important aerospace propellant 1,1-dimethylhydrazine and the 1,2-isomer widely used in experimental carcinogenesis research are cleaved in >90% yield (i.e., to dimethylamine in reaction XII-1 and methylamine in example XII-11, respectively). Similar results for the osazone-forming reagent, phenylhydrazine (reaction XII-13), show that monosubstituted arylhydrazines are amenable to reduction under these conditions. Reduction also occurs with carboxylic acid hydrazides, although it appears to be somewhat more sluggish than with the alkyl- and arylhydrazines; thus iproniazid was reduced to a carboxamide (reaction XII-18), but the pyridyl ring was saturated first and it took several days of room-temperature reduction for the hydrazide function to disappear completely.

Azo compounds are reductively cleaved to primary amines, as in reaction XII-15. This outcome appears to be straightforward with the bisaryl-substituted compounds, no evidence of benzidine or other skeletal rearrangement products having been observed in the azo- or hydrazoarene reductions summarized in Table XII; this is presumably a result of avoiding the acidic conditions necessary for the benzidine rearrangement when using this reducing combination. Extrapolation of these results to the aliphatic analogues leads to the prediction that azoalkanes should also be reducible to primary amines as occurred with the azo compound tautomers (the hydrazones) discussed in section III.A.6. More direct evidence is needed before this prediction can be evaluated, as the one relevant reaction cited in Table XII was reported to take a considerably more complicated course; the mixed aromatic–aliphatic azo compound used as starting material in reaction XII-21 was said to be converted to an α-hydroxy amide with con-

comitant loss of a carbon atom. If the reported structures can be confirmed, XII-21 may provide an interesting example of a nickel–aluminum reduction accompanied by skeletal reorganization, including possibly both a retro-Claisen fragmentation and a hydride shift as well as N–N bond cleavage. Results with the azoxy function have proven straightforward thus far, however, both an azoxyalkane (reaction XII-22) and an azoxyarene (XII-23) being cleaved to the primary amines in high yield.

Triazenes are also conveniently converted to the corresponding amines by treatment with nickel–aluminum alloy in basic medium, as revealed in the data of Table XIII. Most of the specific reactions reported thus far have involved 1-aryl-3-p-tosyl triazenes (e.g., reaction XIII-3), but success has been forthcoming with 1-aryl-3-alkyl- and 1-aryl-3,3-dialkyl-substituted starting materials as well (reactions XIII-1 and XIII-2, respectively). Since these triazenes can be prepared from the corresponding lithium compounds or Grignard reagents, which are readily accessible from halides or hydrocarbons, this method constitutes a procedure for converting hydrocarbons or halides to amines.[120] Interestingly, these reductions could be conducted in preparatively significant yield without extensively affecting certain other functional groups in the molecule, including the carbon–chlorine bond that survived reaction XIII-11. As to tetrazenes, the 1,1,4,4-tetramethyl compound has been reduced to the secondary amine in near-quantitative yield (reaction XIII-21).

The finding that the N-alkoxy group was reductively displaced from an N-nitrosoalkoxylamine derivative in reaction XI-10, as discussed earlier in this section, suggested that other hydroxylamine ethers might similarly be cleaved under these conditions. This prediction was tested by treating N,O-dimethylhydroxylamine with nickel–aluminum alloy in base in reaction XIII-23; the expected products, methylamine and methanol, were found in abundance. The reaction proceeded as smoothly with the free N-hydroxy compounds as it did with the hydroxylamine ether; thus N-methylhydroxylamine and N,N-diethylhydroxylamine were preparatively converted to the primary and secondary amine hydrochlorides, as summarized in reactions XIII-22 and XIII-24, respectively.

These results suggested in turn that N-oxides (i.e., the N,N,N-trisubstituted hydroxylamine derivatives) should be convertible in good yield to the tertiary amines under these conditions. This proved to be the case. As shown in XIII-25, trimethylamine oxide was

TABLE VII. Cleavage of Carbon–Oxygen Bonds Using Nickel–Aluminum Alloy in Base[a]
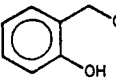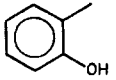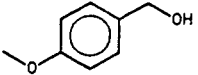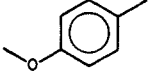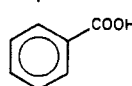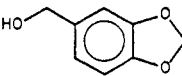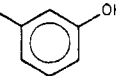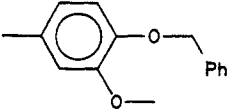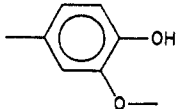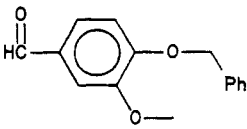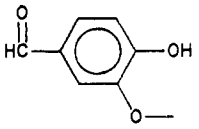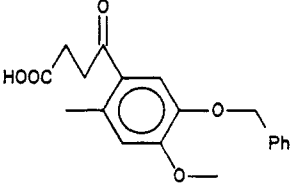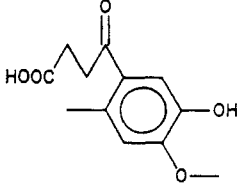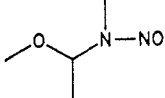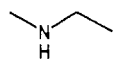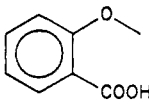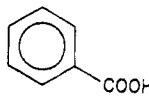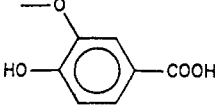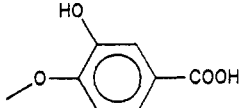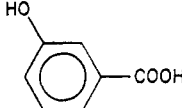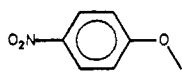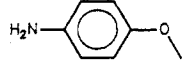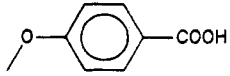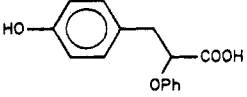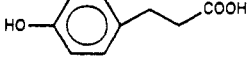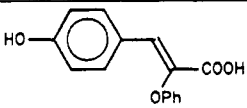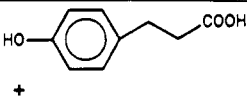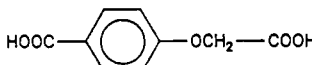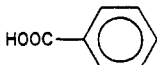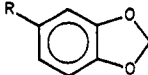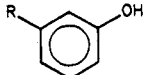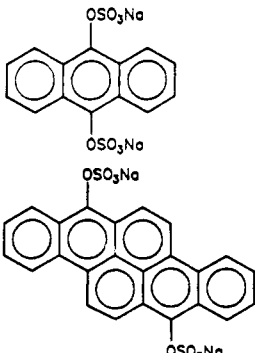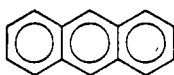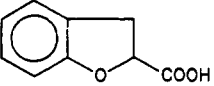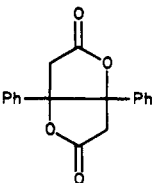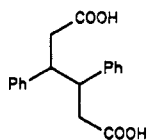
reaction no.	starting material	product(s)	yield, %	comments	ref
VII-1	PhCH₂OH	PhCH₃	70		47
VII-2			85		47
VII-3			50		29
			15		
			20	Schwenk et al. speculate that benzoic acid is produced by initial dehydrogenation to p-methoxybenzaldehyde followed by a Cannizzaro reaction and methoxy group displacement	
VII-4			75		43, 81
VII-5			95		82
VII-6			60		82
VII-7			95		82
VII-8			89		83
VII-9			100		29
VII-10		no reaction			29
VII-11			50		29
VII-12		PhNH₂	20		29
			70		
VII-13		PhCOOH	100		29
VII-14			10	plus 58% recovered starting material	66
		PhOH	none given		

TABLE VII (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
VII-15*	HO—⟨⟩—(OPh)C=CH–COOH	HO—⟨⟩—CH₂CH₂COOH	39		66
		+ PhOH	13		
VII-16	PhOCH₂COOH	PhH	34	plus 66% recovered starting material	48
VII-17	HOOC—⟨⟩—OCH₂—COOH	HOOC—⟨⟩	90		48
VII-18	R = H	R = H	65		43, 81
VII-19	R = Me	R = Me	40	plus 40% recovered starting material	43, 81
VII-20	R = COOH	R = COOH	80		43, 81
VII-21	R = CH₂COOH	R = CH₂COOH	75		43, 81
VII-22	(OSO₃Na anthracene disulfate)	(anthracene)	85	product was obtained after dehydrogenating intermediates	84
VII-23	(OSO₃Na polycyclic trisulfate)	(polycyclic)	80	product was obtained after dehydrogenating hexa- and decahydro intermediates	84
VII-24	(dihydrobenzofuran-2-carboxylic acid)	no reaction			48
VII-25	(Ph-substituted dioxane dione)	(Ph-substituted diacid)	44	meso stereochemistry	37
VII-26	Ph₂O	no reaction			29

ᵃ For instances where carbon–oxygen bonds are cleaved, see also I-40, I-41, I-47, I-48, I-49, II-12, II-25, II-39, II-41, II-43, III-16, III-31, III-66, III-67, III-68, III-71, V-23, XI-11, XI-12, XI-13, XI-15, XI-16, XI-17, XI-18, and XI-19. Instances where a carbonyl is completely reduced to the hydrocarbon also constitute carbon–oxygen bond cleavages (see examples in Table III). Instances where carbon–oxygen bonds are not cleaved can be found in other tables but are not listed here. Only one stereoisomer is shown for convenience for entries marked with an asterisk. Actual materials encountered experimentally may have been of different configuration.

quantitatively deoxygenated by nickel–aluminum alloy in base. Deoxygenation of pyridine N-oxides was discussed in section III.A.2 and appears to be a general reaction. However, some complications that may intervene are described in the next section.

5. Cleavage of Carbon–Carbon and Carbon–Nitrogen Bonds

While C–C and C–N bonds are usually not ruptured during exposure to nickel–aluminum alloy in base, such cleavages can occur under certain circumstances.[20,29,53,61,69,78,121,122] Several examples are summarized in Table XIV.

Reaction XIV-20, for instance, involves loss of a two-carbon fragment concomitant with reductive conversion of an α,α′-diketo azo compound to an alkanolamine. This fragmentation of a C–C linkage may be the result of attack by hydroxide ion on the acetyl carbonyl followed by loss of acetic acid to give an azo-

substituted enolate before reduction can occur. The isolation of 4-methoxypyridine as the major product in the reduction of 4-nitropyridine N-oxide in methanol (reaction XIV-12) can similarly be explained in terms of attack by a nucleophile derived from the solvent on the activated 4-position of the pyridine N-oxide ring, leading to cleavage of the C–N bond by displacement of the nitro group prior to reduction of the N-oxide function.[20]

Carbon–nitrogen bond cleavage is also possible when the nitrogen is in the benzylic position, as in the debenzylation of N-benzylanthranilic acid (reaction XIV-22). Conversion of 1,5-dinitronaphthalene to a mono-aminotetralin in reaction XIV-11 may be an analogous example if hydrogenation of the aromatic ring precedes hydrogenolysis of the C–N linkage. The mechanism of carbon–nitrogen bond cleavage in the reduction of the quaternary ammonium starting material of reaction XIV-16 also appears to involve hydrogenolysis of an
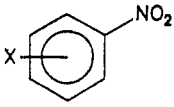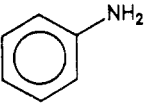
TABLE VIII. Removal of Halogen Atoms from Organic Compounds Using Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
VIII-1	R = H, X = Br	R = H	100		29
VIII-2	R = 4-OCH₂COOH, X = Cl	R = OCH₂COOH	60		85
VIII-3	R = 4-OH, X = Cl	R = OH	70		85
VIII-4	R = 2-NH₂, X = Cl	R = NH₂	77		23
VIII-5	R = 3-NH₂, X = Cl	R = NH₂	84		23
VIII-6	R = 4-NH₂, X = Cl	R = NH₂	75		23
VIII-7		PhNH₂	65		29
VIII-8		PhCH₃	60		29
		PhOH			
VIII-9	X = Cl		100		86
VIII-10	X = Br		100	at 80 °C reaction temperature some cyclohexane was obtained	87
VIII-11	R = 4-OH, X = 3,5-Br₂	R = 4-OH	96		88
VIII-12	R = 3-Me-4-OH, X = 5-Cl	R = 3-Me-4-OH	96		88
VIII-13	R = 2-Me-4-OH, X = 3,5-Cl₂	R = 2-Me-4-OH	93		88
VIII-14	R = 3-t-Bu-4-OH, X = 5-Br	R = 3-t-Bu-4-OH	62		87
VIII-15	R = 2-OH, X = 5-Cl	R = 2-OH	50		89, 90
VIII-16	R = 2-OH, X = 5-Br	R = 2-OH	50		89
VIII-17	R = 2,4-Me₂-6-OH, X = 3-Cl	R = 2,4-Me₂-6-OH	none given		89
VIII-18*			none given		49
VIII-19			97		19
VIII-20	RI	I⁻	quantitative		60
VIII-21			none given		91
VIII-22			97		92
VIII-23			46		93
VIII-24			75		93
VIII-25			87		94

TABLE VIII (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
VIII-26			55		89
VIII-27			none given		89
VIII-28			40		89
VIII-29			50		85
VIII-30			72		85
VIII-31			72		85
VIII-32	RX	no reaction occurs in aqueous formic acid			50
		PhCOOH			
VIII-33	X = 3-Cl		100		29
VIII-34	X = 4-F		60		85
VIII-35	X = 2-Cl-5-F		70		85
VIII-36	X = 2-Cl		55		85
VIII-37	X = 3,4-Cl$_2$		75		85
VIII-38	X = 4-Br		70		85
VIII-39	X = 2,4-Cl$_2$		70		85
VIII-40	X = 2-Cl		ca. 60		85
VIII-41	X = 4-Br		ca. 60		85
VIII-42	X = 3,4-Cl$_2$		ca. 60		85
VIII-43	X = 2,4-Cl$_2$		ca. 60		85
VIII-44	$BrCH_2(CH_2)_9COOH$	$CH_3(CH_2)_9COOH$	100		95
VIII-45	$CH_3CHBr(CH_2)_8COOH$	$CH_3(CH_2)_9COOH$	100		95
VIII-46	$CH_3(CH_2)_8CHBr(CH_2)_7COOH$	$CH_3(CH_2)_{16}COOH$	100		95
VIII-47	$CH_3(CH_2)_{15}CHBrCOOH$	$CH_3(CH_2)_{16}COOH$	100		95
VIII-48	$CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOH$	$CH_3(CH_2)_{16}COOH$	100		95
VIII-49			93		96
VIII-50			91		96

TABLE VIII (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
VIII-51	X = 2-Cl		100		23
VIII-52	X = 3-Cl		94		23
VIII-53	X = 4-Cl		94		23
VIII-54	ClCH$_2$CH$_2$OH	CH$_3$CH$_2$OH	86		23
VIII-55	BrCH$_2$CH$_2$OH	CH$_3$CH$_2$OH	82		23
VIII-56	ClCH$_2$CH$_2$NH$_2$	CH$_3$CH$_2$NH$_2$	100		23
VIII-57	BrCH$_2$CH$_2$NH$_2$	CH$_3$CH$_2$NH$_2$	93		23
VIII-58	ClCH$_2$COOH	CH$_3$COOH	100		23
VIII-59	Cl$_3$CCOOH	CH$_3$COOH	100		23

[a] For instances where halogens are removed, see also I-50, II-35, II-42, II-49, III-29, III-30, III-65, V-24, V-25, VI-17, XV-31, XV-32, XV-33, XV-36, XV-37, XV-38, XV-39, XV-40, XV-41, XV-42, XV-43, XV-44, XV-45, XV-47, XV-48, XV-49, XV-50, XV-51, XV-52, and XV-53. For instances where halogens are not removed, see also IX-39, XIII-10, and XIII-11.

activated benzylic bond; an alternative pathway initiated by base-induced elimination followed by hydrogenation of the resulting olefin to the observed product is ruled out by Sugasawa and Ushioda's report that Hofmann degradation of the starting onium ion resulted in demethylation rather than olefin formation.[121]

Neither Hofmann elimination to olefinic intermediates nor benzylic activation can be responsible for C–N cleavage in some quaternary ammonium ions, however. In reaction XIV-14, the betaine produced on permethylation of anthranilic acid was rapidly converted to benzoic acid. In this case, direct reductive cleavage of an aryl–nitrogen bond would appear to provide the only plausible explanation for the observed results.

Returning to carbon–carbon bond cleavages, Schwenk et al. have shown that they can also occur when aryl ketones and aldehydes containing two oxygen substituents suitably situated on the aromatic ring are treated with nickel–aluminum alloy in base as in reactions XIV-1 to XIV-9. Formyl or acetyl substituents are replaced by hydrogen in 70–75% yield when ortho or para to one of the oxygen substituents (examples XIV-5 and XIV-6), but yields drop to 15–45% when the oxygen substituents are both ortho and para to the carbonyl (as in reactions XIV-2 and XIV-8). The mechanism of this interesting fragmentation, which could hypothetically be solvolytic and/or reductive based on the limited information at hand, has not as yet been explored.

Another C–C bond cleavage of uncertain mechanism involves the displacement of a hydroxymethyl group from the substituted catechol ether used as starting material in reaction XIV-10. Production of guaiacol in 60% yield could have resulted from direct hydrogenolysis of the carbon–carbon bond, from solvolytic displacement of hydroxymethyl as methanediol, from partial dehydrogenation to the aldehyde whose formyl group is displaced as in the previous paragraph, or from a combination of these pathways. It is also possible that a retrograde Lederer–Manasse reaction is involved, with the reaction being driven toward completion by removal of formaldehyde via reduction to methanol. Elucidation of this reaction's mechanism could be profitable, as the 60% yield suggests considerable preparative potential; testing the various hypothetical pathways should make it possible to extrapolate the results to previously unstudied systems.

6. Miscellaneous Reactions

The carbon–metal bond in phenylmercuric acetate is cleaved on treatment with nickel–aluminum alloy in base, as indicated in reaction XIV-21. Biphenyl was observed in unspecified yield as the product. A carbon–arsenic bond was also reported to be cleaved by nickel–aluminum alloy, as in reaction XIV-19. In neither case was the preparative significance indicated, nor was it clear whether the reaction was a hydrogenolysis rather than a nonreductive transformation such as a solvolysis or disproportionation. Clearly, more work aimed at understanding these interesting reactions will be needed.

C. Management of Selectivity

It is frequently possible to limit the reducing action of nickel–aluminum alloy to a subset of the functional groups in a molecule or mixture while leaving others unaffected.

An obvious approach to achieving such selectivity is to make proper use of the structure–reactivity relationships inherent in the data presented above. While few generalizations of universal validity can be inferred from the literature at this stage of progress, the following trends can be noted: carbon–sulfur, carbon–halogen, nitrogen–nitrogen, and nitrogen–oxygen linkages are easily cleaved by treatment with nickel–aluminum alloy in base, while bonds between carbon on the one hand and oxygen, nitrogen, or carbon on the other can only be ruptured when certain activating influences prevail; carbon–carbon and carbon–nitrogen multiple bonds are often saturated with ease, but carbon–oxygen double bonds are reducible only in aldehydes and ketones (esters, amides, and carboxylic acids apparently being inert to reduction); among carbocyclic aromatic rings, benzene derivatives are seldom saturated while naphthalenes frequently undergo partial hydrogenation; in the heteroaromatic series, furans are usually hydrogenated and/or hydrogenolyzed with facility, and thiophenes are the synthetic equivalent of the corresponding saturated acyclic, four-carbon chain. The reduction of pyridines is generally promoted by substituents in the 2-position and by electron-withdrawing substituents in the 3- and 4-positions and is retarded by electron-supplying groups in the 3- and 4-positions.[20] The reactivity of other five- and six-

membered nitrogen heterocycles varies with the structure of the individual compound.

Gradations in reactivity within these broad categories may also be exploited in many cases. Thus, 2-vinylpyridine was first reduced to 2-ethylpyridine and then to 2-ethylpiperidine.[23] Triazenes were reduced to amines in reactions XIII-10 and XIII-11 while chlorine remained in the molecule. On the other hand, 3-chloropyridine was reduced to pyridine (81%) before further reduction to piperidine occurred (reaction II-49). Benzylic ethers were hydrogenolyzed in reactions VII-6 and VII-7 while the aldehyde and ketone functions were reportedly left intact. Reduction of the nitrile in reaction IV-7 could be accomplished without hydrogenation of the aromatic ring. Such differential reactivity of functional groups allows some reductions to proceed in a stepwise fashion. For example, nitrosamines (N-NO) have been observed as intermediates in the reduction of nitramines (N-NO$_2$) (e.g., XI-20), and hydrazines were established as intermediates in the reduction of nitrosamines (e.g., XI-1).

Even with similar functional groups differential reactivity can sometimes be exploited for achieving selectivity. Thus, only three double bonds of cyclooctatetraene were found to be hydrogenated by nickel–aluminum alloy in base, cyclooctene being produced in 90–95% yield in reaction I-27.

Selectivity can also be programmed by controlling reaction time. Early termination of iproniazid reduction yielded the piperidyl hydrazide as the major product of reaction II-66 while the N–N bond was cleaved to a significant extent only after several days under the conditions employed.

Varying reaction temperatures provides another approach to management of selectivity. The methylenedioxy ring of the starting cinnamate used in reactions I-40 and I-41 was cleaved extensively during hydrogenation of the double bond when the reduction was conducted at 50–95 °C but 20–25% of the olefin reduction product in which the methylenedioxy ring was intact remained when the reaction was run at 20–30 °C. Reduction of salicylaldehyde gave the benzylic alcohol at 10–20 °C (III-61) but o-cresol at 90 °C (III-62). o-Benzoylbenzoic acid was reduced in 80% yield to the hydrocarbon (o-benzylbenzoic acid) at 90 °C but to the carbinol lactone (3-phenylphthalide) in 80% yield at 10–20 °C (reaction III-39).

Selectivity can also be arranged by varying the solvent. In reaction III-33, for example, only one of the two keto groups was reduced in the presence of toluene alone while both were reduced when ethanol was also present. No reduction was observed in the absence of organic solvent.[47] Use of toluene as a cosolvent in example I-51 permitted dibenzalacetone to react with nickel–aluminum alloy in base, whereas no reaction occurred in aqueous medium with or without addition of alcohol; if the identity of the reported product is confirmed, reaction I-51 would represent a rare and interesting example of carbon–carbon bond *formation* via reductive coupling induced by this reagent combination.[47] Carbon–nitrogen cleavage leading to replacement of the 4-substituent by alkoxide was observed when 4-nitropyridine N-oxide was reduced in the presence of an alcohol (reactions XIV-12 and XIV-13) but not in aqueous alkali alone (II-79).

On the subject of solvent mixtures, we have enjoyed excellent success in reducing substrates that are poorly soluble in aqueous media and have experienced no difficulty with preparative-scale reductions of such water-insoluble compounds as N-nitrosodiphenylamine and N,N'-dinitrosopiperazine when we added a methanolic solution of the substrate to an equal volume of 1 M potassium hydroxide.[110–113] We have been able to effect facile, quantitative reduction of nitrosamines also in biphasic mixtures (e.g., water/hexane) and even in the presence of solvents such as dichloromethane and dimethyl sulfoxide which contain atoms (halide and sulfur) expected to compete strongly with the nitrosamine for reducing agent.[112]

Directing reductions along a desired course can sometimes be accomplished by addition of extra reagents or catalysts. For example, the presence of ammonia diverts the reduction of ketones toward reductive amination, giving the primary amine.[19] Saavedra has shown that yields of N-alkylalkanolamines produced by hydrogenolysis of N-nitrosooxazolidines can be improved by adding aldehyde after reduction is under way.[114]

Reaction course can also be usefully altered by varying the pH. The presence of base can be an asset, as in Sukh Dev's one-step conversion of an α,β-unsaturated ester to the desired saturated acid (reaction I-28) and in the reduction of 1,2-diphenylhydrazine to aniline (reaction XII-12) without producing any carcinogenic benzidine. However, it can also be a liability. For instance, carbinols are sometimes observed among the reduction products of hydrazones (reaction VI-15), presumably because this functional group suffers base-catalyzed hydrolysis before reduction can occur. Tyman has developed two approaches to overcoming such difficulties. In one of these, smooth reduction is achieved in neutral medium at elevated temperatures,[19] an approach that led to one of the few reports describing saturation of a phenyl ring by nickel–aluminum alloy. Tyman's second approach is to add the aqueous alkali-metal hydroxide to the continuously stirred mixture of alloy and substrate solution.[19] This inverse addition technique has the powerful advantages of not only lowering the pH but also suppressing the escape of hydrogen from the medium, thereby facilitating control of the reaction's stoichiometry.

One of the most dramatic means of altering the relative reactivity of various functional groups toward nickel–aluminum alloy is to replace the alkali-metal hydroxide with formic, acetic, of hydrochloric acid, a comparatively neglected option. The reducing action appears to be limited to nitriles (Table IV) and nitro compounds (Table X) in acidic media. Unlike the corresponding reductions in aqueous base, nitriles are converted to aldehydes, and the primary amines produced on reduction of the nitro group are often N-formylated when formic acid is present. Nitro was reduced in preference to the cyano function when both were present in the same starting material.[50] Yields approached 100% except for aliphatic nitriles, whose aldehyde products may have undergone aldol condensation or other yield-diminishing reactions after formation, and some ortho-substituted aromatic substrates, whose reactive moieties may have been relatively inaccessible for steric reasons. Other functional

TABLE IX. Extrusion of Sulfur from Organic Compounds Using Nickel–Aluminum Alloy in Base[a]
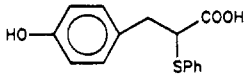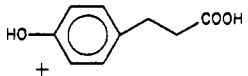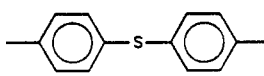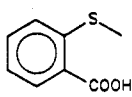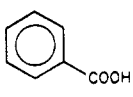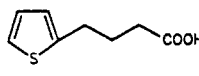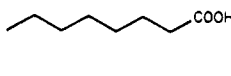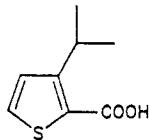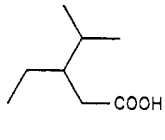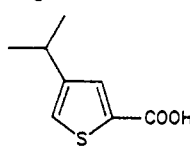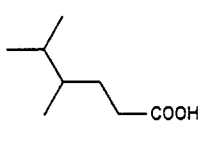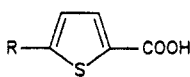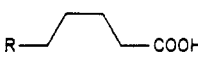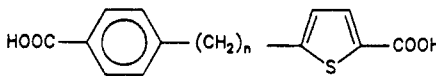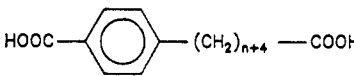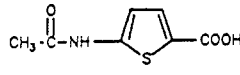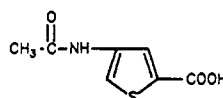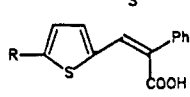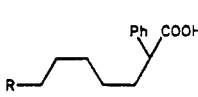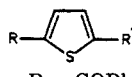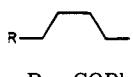
reaction no.	starting material	product(s)	yield, %	comments	ref
	RSH	RH			
IX-1	R = benzyl	R = benzyl	62		66
IX-2	R = o-carboxyphenyl	R = o-carboxyphenyl	96		66
IX-3	R = p-tolyl	R = p-tolyl	81		66
IX-4			73		66
		+	none given		
IX-5			60		66
IX-6			75		29
IX-7			39	plus 44% starting material	97
IX-8			none given		98
IX-9			none given		98
IX-10	R = Et	R = Et	79		99
IX-11	R = CH$_2$CH$_2$Ph	R = CH$_2$CH$_2$Ph	75		100
IX-12	R = CH$_2$CH$_2$CH$_2$Ph	R = CH$_2$CH$_2$CH$_2$Ph	82		100
IX-13	R = (CH$_2$)$_4$Ph	R = (CH$_2$)$_4$Ph	85		100
	HOOC—⟨ ⟩—(CH$_2$)$_n$—[thiophene]—COOH	HOOC—⟨ ⟩—(CH$_2$)$_{n+4}$—COOH			
IX-14	n = 3	n = 3	79		100
IX-15	n = 4	n = 4	82		100
IX-16		H$_2$N(CH$_2$)$_4$COOH	none given		45
IX-17		CH$_3$CH(NH$_2$)(CH$_2$)$_2$COOH	none given		45
IX-18*	R = H	R = H	75		45
IX-19*	R = 2-phenylethyl	R = 2-phenylethyl	70		46
IX-20*	R = 3-phenylpropyl	R = 3-phenylpropyl	63		46
IX-21	R = COPh R′ = H	R = COPh R′ = H	none given		101
IX-22	R = n-pentyl R′ = CO(CH$_2$)$_7$COOH	R = n-pentyl R′ = CO(CH$_2$)$_7$COOH	84		102
IX-23	R = CO(CH$_2$)$_8$COOH R′ = n-Bu	R = CO(CH$_2$)$_8$COOH R′ = n-Bu	44		101, 102
IX-24	R = CO(CH$_2$)$_8$CH$_3$ R′ = (CH$_2$)$_7$COOH	R = CO(CH$_2$)$_8$CH$_3$ R′ = (CH$_2$)$_7$COOH	17		102
IX-25	R = (CH$_2$)$_8$COOH R′ = CO(CH$_2$)$_7$CH$_3$	R = (CH$_2$)$_8$COOH R′ = CO(CH$_2$)$_7$CH$_3$	28		102
IX-26	R = (CH$_2$)$_3$COOH R′ = (CH$_2$)$_8$COOH	R = (CH$_2$)$_3$COOH R′ = (CH$_2$)$_8$COOH	75		103

TABLE IX (Continued)
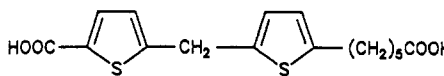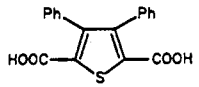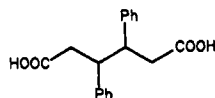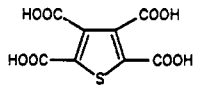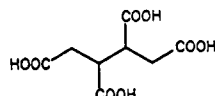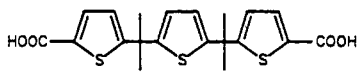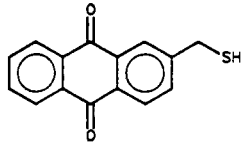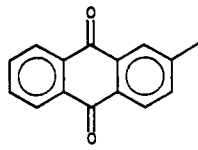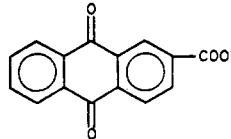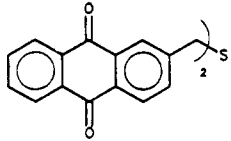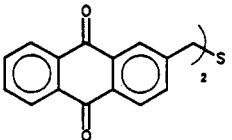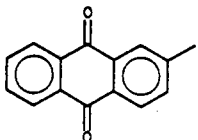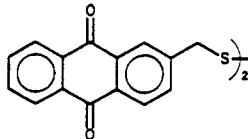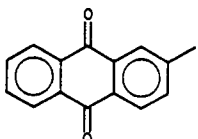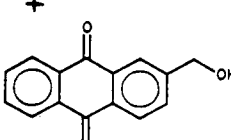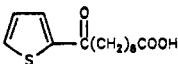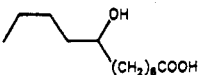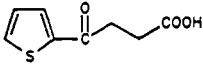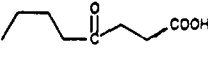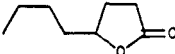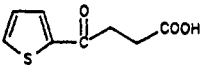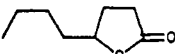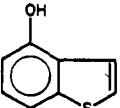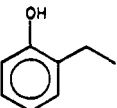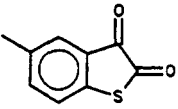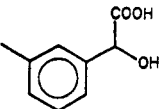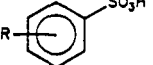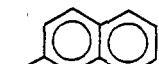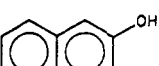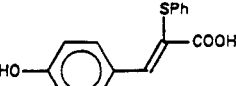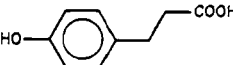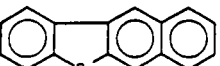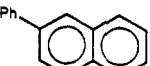
reaction no.	starting material	product(s)	yield, %	comments	ref
IX-27	R = $(CH_2)_5COOH$ R′ = $(CH_2)_8COOH$	R = $(CH_2)_5COOH$ R′ = $(CH_2)_8COOH$	75		103
IX-28	R = R′ = $(CH_2)_8COOH$	R = R′ = $(CH_2)_8COOH$	68		103
IX-29	HOOC—(thiophene)—CH_2—(thiophene)—$(CH_2)_5COOH$	$HOOC(CH_2)_{14}COOH$	65		103
IX-30*	3,4-diphenylthiophene-2,5-dicarboxylic acid derivative	HOOC–CH_2–CH(Ph)–CH(Ph)–CH_2–COOH	78		104
IX-31*	thiophene-2,3,4,5-tetracarboxylic acid	tetracarboxylic open product	none given		104
IX-32	HOOC—[bis-thiophene with $C(CH_3)_2$ bridges]—COOH	$HOOC[(CH_2)_4C(CH_3)_2]_2(CH_2)_4COOH$	80		104
IX-33	2-(mercaptomethyl)anthraquinone	2-methylanthraquinone	13	reduction was performed with alloy and substrate in a 1:1 ratio	55
		+ anthraquinone-2-carboxylic acid	12		
		+ 2-(hydroxymethyl)anthraquinone	6		
		+ bis[(anthraquinon-2-yl)methyl] disulfide	19		
IX-34	bis[(anthraquinon-2-yl)methyl] disulfide	2-methylanthraquinone	69		55
IX-35	bis[(anthraquinon-2-yl)methyl] ...	2-methylanthraquinone	20		55
		+ anthraquinone-2-carboxylic acid	16		
		+ 2-(hydroxymethyl)anthraquinone	9		

TABLE IX (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
IX-36*		PhCOOH + PhCO(CH₂)₂COPh + Ph(CH₂)₄Ph	trace 1–12 0–76	yield depended on amount of alloy added	56, 105
IX-37		PhCOOH	8		105
IX-38*		$\left(\text{EtO}-\text{C}_6\text{H}_4-\text{CO}-\text{CH}_2\right)_2$ + EtO—C₆H₄—COOH	79 2	plus 1% starting material	105
IX-39*		(see structures)	4 7 41		56
IX-40*		(see structure) + C₁₀H₁₁(CH₂)₄C₁₀H₁₁	33 54		56
IX-41*		(see structure)	10		56
IX-42		(see structure)	none given		106
IX-43		(see structure)	70		107

IX-38 product: $\left(\text{EtO}-\!\!\bigcirc\!\!-\overset{O}{\overset{\|}{C}}-CH_2\right)_2$

$+$

EtO—◯—COOH

TABLE IX (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
IX-44	[thiophene-C(O)(CH₂)₈COOH structure]	[CH₃CH₂CH₂CH(OH)(CH₂)₈COOH structure]	88		66
IX-45	[thiophene-C(O)CH₂CH₂COOH structure]	[ketone + COOH structure]	38		66
		[lactone structure]	30		
IX-46	[thiophene-C(O)CH₂CH₂COOH structure]	[lactone structure]	76	reaction IX-45 gave two products but only this product was obtained when reaction was heated at 70–80 °C overnight	66
IX-47	[benzothiophene-OH structure]	[2-ethylphenol structure]	71		66
IX-48	[methyl benzothiophene dione structure]	[mandelic acid type structure]	70		66
IX-49	R = H	R = H	10		29
IX-50	R = 2-COOH	R = COOH	40		29
IX-51	R = 3-COOH	R = COOH	50		29
IX-52	[naphthalene-SO₃H structure]	[naphthalene structure]	40		29
IX-53	[HO-naphthalene-SO₃H structure]	[HO-naphthalene structure]	30		29
IX-54	[HO₃S-naphthalene-OH-SO₃H structure]	[naphthalene-OH structure]	30		29
IX-55	ArSO₂NH₂	no reaction		in aqueous formic acid	18
IX-56*	[HO-phenyl-C(SPh)=CH-COOH structure]	[HO-phenyl-CH₂CH₂-COOH structure]	82		66
IX-57	[dibenzoselenophene structure]	[Ph-naphthalene structure]	none given	by distillation from a mixture of Raney alloy powder with zinc	108

[a] For instances where sulfur is extruded, see also II-32, III-34, III-51, XV-25, XV-26, XV-27, XV-28, XV-29, XV-30, XV-31, XV-32, XV-33, XV-34, XV-35, XV-36, and XV-53. Only one stereoisomer is shown for convenience for entries marked with an asterisk; actual materials encountered experimentally may have been of different configuration.
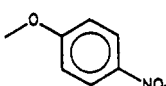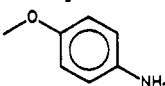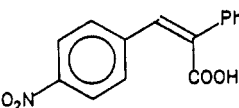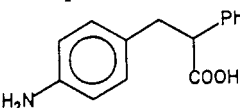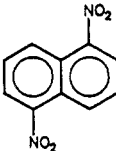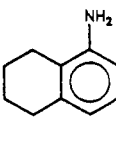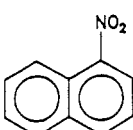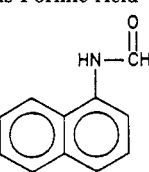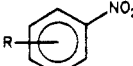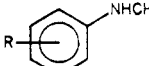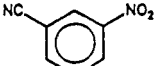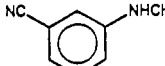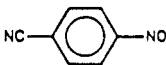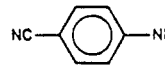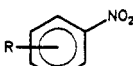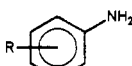
groups that are easily reduced in alkaline media are inert to nickel–aluminum alloy in acid, including olefinic double bonds, pyridyl and naphthyl rings, carbon–halogen, –oxygen, and –sulfur bonds, aldehydes, and ketones. Oximes and imines are hydrolyzed without reduction.[50]

Changing the alloy/substrate ratio provides another route to achieving selectivity. One approach has been to add only enough alloy to effect the most favored reduction(s). For instance, aluminum (as the alloy) and substrate were mixed in a mole ratio of 4:3 in reducing hydrazones to amines without hydrogenolyzing sulfonic

acid or furan moieties elsewhere in the molecule (reaction VI-10). Adding the alloy in portions may be especially useful in desulfurization reactions, which, like those effected with preformed Raney nickel, appear to be susceptible to strong retardation via poisoning of the spongy metal surface as the reaction progresses; for example, removal of the keto oxygen atoms in reaction IX-36 did not occur until a second portion of alloy was added.

Another possible approach to management of selectivity is to replace the reductant with some other alloy of aluminum. Thus copper–aluminum alloy, though

TABLE X. Reduction of C-Nitroso and C-Nitro Compounds with Nickel–Aluminum Alloy under Basic versus Acidic Conditions[a]

reaction no.	starting material	product(s)	yield, %	ref
		In Base		
X-1	PhNO	PhNH₂	104	110
X-2		+ PhNH₂	70 / 20	29
X-3*			68	52
X-4			52	53
X-5	PhNO₂	PhNH₂	84	23
		In Aqueous Formic Acid		
X-6			90	50
X-7	R = H	R = H	86	50
X-8	R = 4-Me	R = 4-Me	80	50
X-9	R = 2-Br	R = 2-Br	80	50
X-10	R = 3-Br	R = 3-Br	85	50
X-11	R = 4-Br	R = 4-Br	85	50
X-12	R = 2-COOH	R = 2-COOH	90	50
X-13	R = 4-COOEt	R = 4-COOEt	95	50
X-14	R = 4-CONH₂	R = 4-CONH₂	90	50
X-15	R = 2-OH	R = 2-OH	50	50
X-16	R = 4-OMe	R = 4-OMe	70	50
X-17	R = 3-NH₂	R = 3-NH₂	100	50
X-18	R = 4-NH₂	R = 4-NH₂	100	50
X-19	R = 4-COCH₃	R = 4-COCH₃	80	50
X-20			90	50
X-21			90	50
		In Aqueous Acetic Acid		
X-22	R = 4-COCH₃	R = 4-COCH₃	98	50
X-23	R = H	R = H	90–100	50
X-24	R = 4-Me	R = 4-Me	90–100	50
X-25	R = 2-NH₂	R = 2-NH₂	90–100	50
X-26	R = 4-Br	R = 4-Br	90–100	50

[a] For other instances of reduction of C-nitro groups under basic conditions, see also II-23, II-33, II-35, II-79, III-28, III-46, VII-12, VIII-7, VIII-51, VIII-52, VIII-53, and XIV-11. An asterisk indicates that the stereoisomer shown is only one of the mixture known to be present.
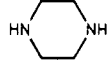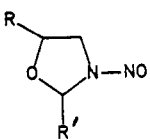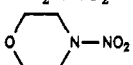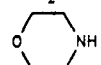
capable of removing chlorine when used in place of its nickel counterpart in reduction of o-chlorobenzoic acid, gave improved isotopic purity of the debrominated product in the dehalogenation of p-bromobenzoic acid in heavy water.[123] Cobalt–aluminum alloy may also be useful in base-induced reductions.[124] However, a de-

tailed consideration of nickel-free reductants is beyond the scope of this review.

IV. Isotopic Labeling

Reduction with nickel–aluminum alloy should in principle furnish one of the most advantageous methods

TABLE XI. Conversion of Nitramines and Nitrosamines to Amines Using Nickel–Aluminum Alloy in Base

reaction no.	starting material	product(s)	yield, %	ref
	$\underset{R'}{\overset{R}{>}}N-NO$	$\underset{R'}{\overset{R}{>}}NH$		
XI-1	R = R' = Me	R = R' = Me	96	111–113
			47	110
XI-2	R = R' = Et	R = R' = Et	92	111–113
XI-3	R = R' = i-Pr	R = R' = i-Pr	96	111–113
XI-4	R = R' = n-Bu	R = R' = n-Bu	99	111–113
			62	110
XI-5	R,R' = -(CH$_2$)$_4$-	R,R' = -(CH$_2$)$_4$-	95	111–113
XI-6	R,R' = -(CH$_2$)$_5$-	R,R' = -(CH$_2$)$_5$-	94	111–113
XI-7	R,R' = -(CH$_2$)$_2$O(CH$_2$)$_2$-	R,R' = -(CH$_2$)$_2$O(CH$_2$)$_2$-	97	111–113
XI-8	R = Ph, R' = Me	R = Ph, R' = Me	100	111–113
			60	110
XI-9	R = R' = Ph	R = R' = Ph	86	110
XI-10	MeO(Me)NNO	MeNH$_2$ + MeOH	93 55	112
XI-11	MeN(NO)CH$_2$OMe	Me$_2$NH + MeNH$_2$	41 54	112
	RCH$_2$N(NO)CH(CH$_3$)OCH$_3$	RCH$_2$NHCH$_2$CH$_3$		
XI-12	R = H	R = H	89	83
XI-13	R = Me	R = Me	86	83
XI-14	ONN⟨ ⟩NNO	HN⟨ ⟩NH	88 78	111–113 110
	$\underset{R'}{\overset{R}{\text{(oxazolidine ring)}}}N-NO$	RCHOHCH$_2$NHCH$_2$R'		
XI-15	R = R' = H	R = R' = H	93	114
XI-16	R = Me, R' = H	R = Me, R' = H	98	114
XI-17	R = H, R' = Me	R = H, R' = Me	31–97	114
XI-18	R = Me, R' = Et	R = Me, R' = Et	53	114
XI-19	R = i-Bu, R' = Me	R = i-Bu, R' = Me	56	114
XI-20	i-Pr$_2$NNO$_2$	i-Pr$_2$NH	100	110, 113
XI-21	O⟨ ⟩N-NO$_2$	O⟨ ⟩NH	92	110, 113

for incorporating hydrogen isotopes into organic molecules. Though the metal is the source of the electrons, the hydrogen atoms transferred come from the solvent. By the simple means of using deuterium oxide or tritiated water to constitute the reduction mixture, it should be possible to synthesize a vast array of labeled hydrogenation and hydrogenolysis products quickly and inexpensively, without the need for an exogenous source of D$_2$ or T$_2$.

Despite its apparent promise, the method has received very little attention in this regard. As summarized in Table XV, only a few references have appeared in the literature that describe the use of nickel–aluminum alloy for isotopic labeling.[61,85,106,107,123–130] Most have involved hydrogenolysis of sulfur compounds, including sulfonic acids (such as reaction XV-22) and thiophene derivatives (example XV-26), or halides, including fluorides (reaction XV-43) as well as chlorides and bromides (e.g., 3-bromo-2,4-dichlorophenol in example XV-38). Remarkably, we have found only two reports of the alloy's use in isotope incorporation via hydrogenation of an unsaturated functional group other than the thiophenes: the olefinic double bond of the thienylacrylic acid in reaction XV-35; and the cyano group of the indolylacetonitrile in example XV-46.

Clearly, the reaction can be successful. Thus, pentachlorophenol was converted to phenol-d_5 in ≥70% chemical yield and an isotopic purity of 97% (reaction XV-39). It seems likely that reactions reported to give lower extents of isotopic incorporation would be made satisfactory if all exchangeable hydrogen were replaced by the desired isotope before the reduction is begun. Unfortunately, however, so few of the reactions reported to use hydrogenation or hydrogenolysis by nickel–aluminum alloy to achieve labeling have included data on the isotopic distribution in the product that generalizations are difficult to make with confidence. Additional exploratory work in this area should expand the method's scope considerably.

Treatment with nickel–aluminum alloy in base induces isotopic exchange in aromatic substrates that can be independent of any reducing action. Thus, aniline (reaction XV-24) was ortho-deuteriated with some stereoselectivity in a reaction that did not occur when the alloy was omitted. Interestingly, all three bromoaniline isomers were reduced to aniline that was mostly ortho-deuteriated (reaction XV-50). When scrambling and/or exchange loss of label are disadvantageous, it may be possible to restore stereoselectivity by using copper–aluminum alloy instead.[123]

V. Decontamination and Disposal of Hazardous Compounds

Responsible decontamination and disposal of hazardous wastes is a matter of growing moral and legal

TABLE XII. Cleavage of Hydrazines, Hydrazides, and Azo and Azoxy Compounds with Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	ref
	R,R′N—NH₂	R,R′N—NH		
XII-1	R = R′ = Me	R = R′ = Me	97	113, 117
XII-2	R = R′ = Et	R = R′ = Et	100	113, 117
XII-3	R = R′ = i-Pr	R = R′ = i-Pr	100	113, 117
XII-4	R = R′ = n-Bu	R = R′ = n-Bu	93	113, 117
XII-5	R,R′ = -(CH₂)₅-	R,R′ = -(CH₂)₅-	89	113, 117
XII-6	R,R′ = -(CH₂)₄-	R,R′ = -(CH₂)₄-	100	113, 117
XII-7	R,R′ = -(CH₂)₂O(CH₂)₂-	R,R′ = -(CH₂)₂O(CH₂)₂-	100	113, 117
XII-8	R = Ph, R′ = Me	R = Ph, R′ = Me	96	113, 117
			75	110
XII-9	H₂NN–piperazine–NNH₂	HN–piperazine–NH	73	117
XII-10	(i-Pr)NHC(O)–C₆H₄–CH₂NHNH–	(i-Pr)NHC(O)–C₆H₄–CH₂NH₂	62	118
		+		
		(i-Pr)NHC(O)–C₆H₄–CH₃	27	
		+		
		CH₃NH₂	97	
	RNHNHR	RNH₂		
XII-11	R = Me	R = Me	94	117
XII-12	R = Ph	R = Ph	101	117
			87	110
	RNHNH₂	RNH₂		
XII-13	R = phenyl	R = phenyl	98	113, 117
XII-14	R = p-tolyl	R = p-tolyl	78	117
XII-15	PhN=NPh	PhNH₂	79	110
XII-16	PhNHNHC(O)NHNHPh	PhNH₂	96	117
	pyridyl-C(O)NHNHR	piperidinyl-C(O)NH₂		
XII-17	R = H		none given	20, 118
XII-18	R = i-Pr		none given	20, 118
XII-19	Ph—N=N—C₆H₄—OH	PhNH₂	100	110
		+		
		HO—C₆H₄—NH₂	88	
XII-20	Ph—N=N—C₆H₄—NH₂	PhNH₂	100	110
		+		
		H₂N—C₆H₄—NH₂	97	
XII-21	Ph-C(O)-CH(CHO)-N=NPh	Ph-CH(OH)-C(O)NH₂	ca. 15	69
	R—N=N(→O)—R	RNH₂		
XII-22	R = methyl	R = methyl	100	110
XII-23	R = phenyl	R = phenyl	86	110
XII-24	R = p-anisyl	R = p-anisyl	58	110

[a] For instances of the cleavage of N–N bonds in pyridazines, see also II-76, II-77, and II-78. For an additional instance of hydrazide cleavage, see also II-65.

concern,[131,132] and nickel–aluminum alloy has been shown to be of considerable value in controlling hazards associated with laboratory operations involving a variety of carcinogens and other hazardous materials. The use of this reducing system to destroy nitrosamines[133] and hydrazines[134] in laboratory waste solutions has been proven reliable through collaborative studies. The method seems equally applicable to other genotoxic compound classes, including hydrazides, azo and azoxy compounds, nitramines, triazenes, tetrazenes, and organic halides.

Dacarbazine (XIII-2), an important antineoplastic agent, can be completely degraded by this method as can the drugs procarbazine (XII-10), iproniazid (XII-18), and isoniazid (XII-17). 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a compound that

TABLE XIII. Reduction of Triazenes, Tetrazenes, Hydroxylamines, Hydroxylamine Ethers, and Amine Oxides with Nickel–Aluminum Alloy in Base^a

reaction no.	starting material	product(s)	yield, %	ref
XIII-1	CH₃NH—N≡N—⬡—CH₃	CH₃NH₂ + ⬡—NH₂ (CH₃-)	84 88	110
XIII-2	imidazole-carboxamide N≡N—N(CH₃)₂	imidazole-carboxamide NH₂ + (CH₃)₂NH	75 86	118
	R—⬡—N̄—N≡NSO₂—⬡—CH₃	R—⬡—NH₂		
XIII-3	R = H	R = H	80–85	119
XIII-4	R = 2-Me	R = 2-Me	82	120
XIII-5	R = 3-Me	R = 3-Me	79	120
XIII-6	R = 4-Me	R = 4-Me	66	120
XIII-7	R = 2,5-Me₂	R = 2,5-Me₂	76	120
XIII-8	R = 2-*t*-Bu	R = 2-*t*-Bu	19	120
XIII-9	R = 2-CH₂Ph	R = 2-CH₂Ph	71	120
XIII-10	R = 3-Cl	R = 3-Cl	41	120
XIII-11	R = 4-Cl	R = 4-Cl	49	120
XIII-12	R = 2-OMe	R = 2-OMe	63–80	119, 120
XIII-13	R = 4-OMe	R = 4-OMe	51	120
XIII-14	R = 4-Ph	R = 4-Ph	62	120
XIII-15	R = 2-CH₂N(CH₃)₂	R = 2-CH₂N(CH₃)₂	52–55	119
XIII-16	R = 2-CONHCH₃	R = 2-CONHCH₃	37–40	119
XIII-17	R = 2-OCH₃-6-CONHCH₃	R = 2-OCH₃-6-CONHCH₃	34–38	119
XIII-18	Ph—C(CH₃)₂—N̄—N≡NSO₂—⬡—CH₃	Ph—C(CH₃)₂—CH₂NH₂	25	120
XIII-19	Ph⌒⌒—N—N̄≡NSO₂—⬡—CH₃	Ph⌒⌒NH₂	25	120
XIII-20	phenanthrene—N̄—N≡N—SO₂—⬡—CH₃	phenanthrene—NH₂	54	120
XIII-21	Me₂NN=NNMe₂	Me₂NH	94	110
XIII-22	MeNHOH	MeNH₂	77	110
XIII-23	MeNHOMe	MeNH₂ + MeOH	88 100	110 110
XIII-24	Et₂NOH	Et₂NH	59	110
XIII-25	Me₃N→O	Me₃N	101	110

^{a} For other instances of the reductive cleavage of N–O bonds in oxazoles and a hydroxylamine ether, see also II-44, II-45, and XI-10. For additional instances of the reduction of amine oxides, see also II-67, II-79, XIV-12, and XIV-13.

produces in animals the symptoms of human Parkinson's disease, can be reduced to the physiologically inactive 1-methyl-4-phenylpiperidine although the reaction was not completely reliable and could not be recommended as a hazard control procedure.[44] The wide range of compounds that can be degraded makes this method particularly valuable for hazard control applications involving mixtures of compounds.

The approach is often far preferable to the alternatives. Reduction of azobenzene yields the potent carcinogen benzidine when the reduction is carried out in acidic medium,[135] but aniline uncontaminated with benzidine is produced when nickel–aluminum alloy in base is used to reduce the hydrazobenzene intermedi-

ate.[117] Oxidative degradation of 1,1-dimethylhydrazine, an important aerospace propellant, can produce the potent carcinogen N-nitrosodimethylamine,[136] but the nickel–aluminum alloy method gives only dimethylamine and ammonia.[112]

Recently, it has been reported[137] that a variety of nitrosamides can be completely degraded by using nickel–aluminum alloy in a reaction medium of gradually increasing pH. No diazoalkanes are generated and the final reaction mixtures are not mutagenic. The precise role of the alloy is obscure but it does appear to suppress the formation of mutagens. Recently, we have enjoyed success using nickel–aluminum alloy in potassium hydroxide solution to completely degrade a

TABLE XIV. Cleavage of Carbon–Carbon, Carbon–Nitrogen, Carbon–Arsenic, and Carbon–Mercury Bonds with Nickel–Aluminum Alloy in Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
XIV-1	R = 3,4-(OMe)$_2$	R = 3,4-(OMe)$_2$	75		29
XIV-2	R = 2,4-(OMe)$_2$	R = 2,4-(OMe)$_2$	45		29
XIV-3	R = 3-OEt-4-OH	R = 3-OEt-4-OH	75		29
XIV-4	R = 2-OH-3-OMe	R = 2-OH-3-OMe	75		29
XIV-5	R = 2,3-(OMe)$_2$	R = 2,3-(OMe)$_2$	70		29
XIV-6	R = 3-OMe-4-OH	R = 3-OMe-4-OH	70		29
XIV-7	R = 3-OH-4-OMe	R = 3-OH-4-OMe	70		29
XIV-8			15	plus some starting material	29
XIV-9			70		29
XIV-10			60		29
XIV-11			52		53
XIV-12			74	methanol as solvent	20
XIV-13			51	ethanol as solvent	20
XIV-14			none given		61
XIV-15			82		78
XIV-16			100		121
XIV-17			none given		121
XIV-18			93		122
XIV-19		PhNH$_2$	none given		29
XIV-20			none given		69
XIV-21	PhHgOAc	Ph–Ph	none given		29
XIV-22			none given		61

[a] For instances of the cleavage of other carbon–nitrogen bonds, see also II-75, XI-11, and XII-10.

variety of antineoplastic agents containing N-nitroso and/or (2-chloroethyl)amino groups; no mutagens are produced with this method, in contrast to several other methods.[23] For example, mechlorethamine was completely degraded by potassium hydroxide solution alone but the reaction mixture was mutagenic. When nickel–aluminum alloy was present, degradation was also complete but no mutagens were detected.[23] Other advantages are summarized in the next section.

While on the subject of hazard control, it should be noted that the reaction gives off flammable hydrogen gas and so it should only be carried out in a properly functioning chemical fume hood. In addition the reaction can exhibit an induction period[58] that can cause the reaction mixture to become very hot or even boil. The reaction should not be performed in a vessel that is more than about one-quarter full; additionally the alloy should be added to the stirred basic solution at a sufficiently slow rate that excessive frothing does not occur. At the end of the reaction the spent nickel is removed by filtration through a pad of Celite. This nickel is potentially pyrophoric but we have experienced no problems. Nevertheless, air should not be sucked through the nickel for long periods, and the nickel should be allowed to dry on a metal tray away from flammable substances for 24 h before disposal. We have observed[23] that the completeness of the reduction may occasionally depend on the cosolvent used. Thus, it is always advisable to consult the original literature before using this procedure in a hazard control application. If the substrate/solvent combination has not been previously investigated, full validation should be performed to prove the method reliable for the application at hand.

VI. Advantages: Comparison with Other Reductants

Nickel–aluminum alloy reductions are especially convenient to perform. Experimentally, the alloy need only be added to an alkaline solution of the substance to be reduced in most cases. Workup is accomplished by filtering to remove the spongy nickel and recovering the product from the filtrate. The catalyst does not have to be prepared beforehand, and special apparatus is not required. (Of course, as with any reaction that could generate hydrogen or other hazardous materials, these reductions should be conducted in an efficient chemical fume hood.)

The alloy is a low-cost reagent, currently retailing in small quantities for 7¢ per gram.[138] It should be borne in mind, however, that nickel–aluminum alloy is in excess in nearly all of the applications described above. When working on a large scale, therefore, it may be preferable to use a purely catalytic alternative.

Since both the catalytic surface and the ultimate reducing agent are generated in situ, closely similar results can be expected from one replicate run to another. In contrast, various Raney nickel preparations can differ greatly in their properties. Moreover, a Raney catalyst can change in activity as it ages, but we know of no such shelf life limitation for nickel–aluminum alloy.

Results can be quite different from those using preformed Raney nickel as a hydrogenation catalyst. For example, Raney nickel was consumed in much larger quantity but gave a somewhat smaller yield of product

than nickel–aluminum alloy when used for reduction IX-44. Papa et al. have observed that Raney nickel can be replaced with a substantially smaller amount of nickel–aluminum powder for some applications.[66] Jones reported that the alloy in hot aqueous alkali (reaction I-27) converted cyclooctatetraene to cis-cyclooctene as the major product, even though Raney nickel hydrogenation gave cyclooctane with no observable evidence of selective reduction to cyclooctene. The author also found evidence suggesting that the dienes produced in the nickel–aluminum alloy reduction of cyclooctatetraene differ stereochemically from those produced in the "normal" catalytic process.

Resistance to rearrangements is another of the procedure's important advantages. While lithium aluminum hydride and related reagents have often been found to convert oximes,[77,78,139–141] hydroxylamines,[141,142] and nitro compounds[142] to mixtures of secondary as well as primary amines, nickel–aluminum alloy reduction produces the primary amine uncontaminated by the rearranged isomer.[77,78] Nor does 1,2-diphenylhydrazine undergo the acid-catalyzed benzidine rearrangement[135] under these conditions, and the Fischer–Hepp rearrangement is not observed with N-nitroso-N-methylaniline (reaction XI-8). Even base-induced transformations such as the benzilic acid rearrangement need not be a problem. Thus, nickel–aluminum alloy in aqueous alkali was found to convert benzil to benzoin containing only traces of benzilic acid.[19]

Nickel–aluminum alloy reduction can be used to give stereochemical results different from those of other reagents. For example, nickel–aluminum reduction of the unsaturated ketone in reaction III-47 gives an alcohol with one configuration while lithium in ammonia gives the alcohol with the opposite configuration.[73] Similarly, reduction of 2-methylcyclohexanone (III-4) gave 90% of the trans alcohol while catalytic hydrogenation over nickel (43%), treatment with lithium aluminum hydride (82%), and reduction with sodium borohydride (69%) gave mixtures that were less pure stereochemically. Nickel–aluminum alloy was found[87] to be more efficient than zinc, tin, or aluminum metal alone for the removal of halides from aromatic compounds.

VII. Summary and Recommendations for Future Work

Nickel–aluminum alloy in base has been shown to be a versatile reducing system, capable of conveniently effecting many interesting transformations. Double and triple bonds have been hydrogenated, and nitriles, oximes, hydrazones, and nitro compounds have been converted to primary amines. Carbonyl compounds can be reduced to the corresponding carbinols or hydrocarbons. Reductive amination is observable when ammonia is used in place of the alkali-metal hydroxide. Hydrogenolysis of numerous Ar-X derivatives to the corresponding Ar-H compounds has proven useful, where X = OR, SR, AsO_3H_2, SO_3H, halide, NR_3^+, and, surprisingly, formyl. Hydrogenolysis of benzylic and certain other carbon–heteroatom bonds has also been reported. Hydrogenolytic ring-opening reactions have been observed with furans, thiophenes, and methylenedioxy compounds, the latter usually involving cleavage of aryl–oxygen as well as CH_2–O bonds.

TABLE XV. Isotopic Labeling Achieved by Treatment with Nickel–Aluminum Alloy in Deuteriated or Tritiated Aqueous Base[a]

reaction no.	starting material	product(s)	yield, %	comments	ref
XV-1[b]	R = H	R = H	1.13 D atoms		61, 123
XV-2[b]	R = 2-NH₂	R = 2-NH₂	1.74 D atoms		61
XV-3[b]	R = 2-NHCH₃	R = 2-NHCH₃	1.12 D atoms		61
XV-4[b]	R = 2-N(CH₃)₂	R = 2-N(CH₃)₂	0.49 D atom		61
XV-5[b]	R = 2-N⁺(CH₃)₃	R = H	2.74 D atoms	product:benzoic acid	61
XV-6[b]	R = 3-NH₂	R = 3-NH₂	1.24 D atoms		61
XV-7[b]	R = 3-N(CH₃)₂	R = 3-N(CH₃)₂	0.33 D atom		61
XV-8[b]	R = 4-NH₂	R = 4-NH₂	0.65 D atom		61
XV-9[b]	R = 4-NHCH₃	R = 4-NHCH₃	0.35 D atom		61
XV-10	R = 4-N(CH₃)₂	R = 4-N(CH₃)₂	no reaction		61
XV-11[b]	R = 2-NHEt	R = 2-NHEt	0.83 D atom		61
XV-12[b]	R = 2-NH-n-Pr	R = 2-NH-n-Pr	1.07 D atoms		61
XV-13[b]	R = 2-NH-n-Bu	R = 2-NH-n-Bu	1.23 D atoms		61
XV-14[b]	R = 2-NHPh	R = 2-NHPh	1.88 D atoms		61
XV-15[b]	R = 2-NHCH₂Ph	R = 2-NH₂	1.19 D atoms	product:anthranilic acid after 1 h at 70 °C	61
XV-16[b]	R = 2-NHCOCH₃	R = 2-NHCOCH₃	3.34 D atoms	0.74 in ring, 2.60 in methyl group	61
XV-17[b]	R = 2-NHCH₂COOH	R = 2-NHCH₂COOH	1.70 D atoms	1.28 in ring, 0.42 in methylene group	61
XV-18[b]			1.13–1.94 D atoms		61
XV-19[b]			2.25 D atoms	1.59 in ring, 0.66 in methylene group	61
XV-20[b]			1.87 D atoms		61
XV-21[b]			0.03 D atom		61
XV-22			16	extent of H–D exchange at C-8 was ca. 70%	126
XV-23			31	extent of H–D exchange was ca. 30%	126
XV-24[b]			none given	mostly ortho; exchange did not occur when the alloy was omitted	127
XV-25		D₂CHCHDCHDCD₂COOH	70		128
XV-26	R = ethyl	R = ethyl	70–95		106
XV-27	R = isopropyl	R = isopropyl	70–95		106
XV-28	R = sec-butyl	R = sec-butyl	70–95		106
XV-29	R = pentyl	R = pentyl	70–95		106
XV-30	R = 2-phenylethyl	R = 2-phenylethyl	70–95		106
XV-31		CD₃CHDCHDCD₂COOH	70–80		125
XV-32		CD₃CHDCHDCD₂COOH	80		125
XV-33		CD₃CHDCD(CD₃)COOH	91		125

TABLE XV (Continued)
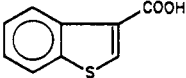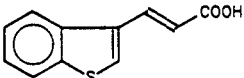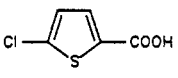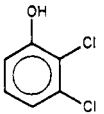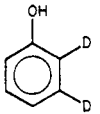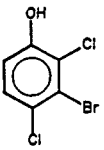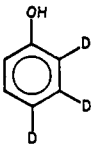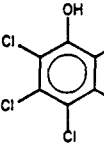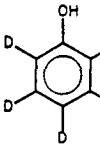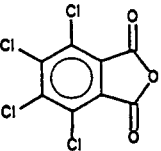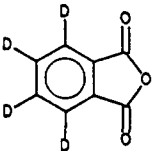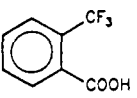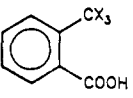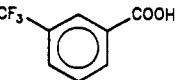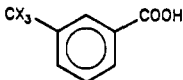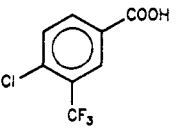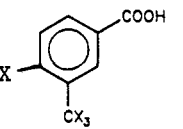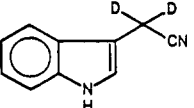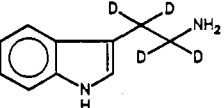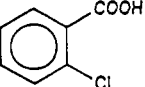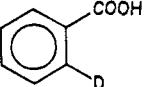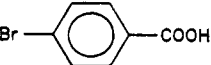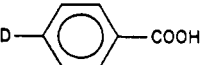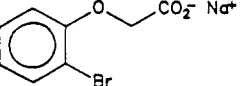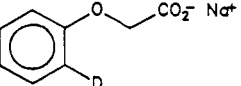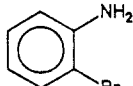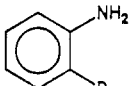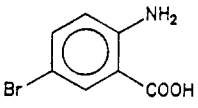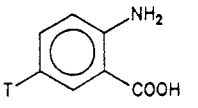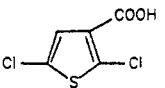
reaction no.	starting material	product(s)	yield, %	comments	ref
XV-34	(benzothiophene-3-CH(COOH) structure)	PhCD(CHD$_2$)COOH	none given		125
XV-35*	(benzothiophene-3-CH=CHCOOH structure)	PhCD(CHD$_2$)CHDCHDCOOH	70		125
XV-36	(5-chlorothiophene-2-COOH structure) Cl—(thiophene)—COOH	CT$_3$CHTCHTCT$_2$COOH	none given		125
XV-37[b]	(2,3-dichlorophenol structure)	(phenol-2,4-d$_2$ structure)	92	contained all isotopomers (d_0–d_5)	129
XV-38[b]	(2-chloro-3-bromo-4-chlorophenol structure)	(phenol-d$_3$ structure)	80	contained all isotopomers (d_0–d_5)	129
XV-39	(pentachlorophenol structure)	(phenol-d$_5$ structure)	70–74	isotopic purity was 97%	85, 129
XV-40	(tetrachlorophthalic anhydride structure)	(tetradeuterophthalic anhydride structure)	78		85
XV-41	CCl$_3$CO$_2$Na	CD$_3$CO$_2$D	17–29	product obtained on workup with deuteriated solvents	85
XV-42	CH$_3$CCl$_2$CO$_2$Na	CH$_3$CD$_2$COOD	22–28	product obtained on workup with deuteriated solvents	85
XV-43	(2-CF$_3$ benzoic acid structure)	(2-CX$_3$ benzoic acid structure)	70	X = H, D, or T	124
XV-44	(3-CF$_3$ benzoic acid structure)	(3-CX$_3$ benzoic acid structure)	70	X = H, D, or T	124
XV-45	(4-chloro-3-CF$_3$ benzoic acid structure)	(4-X-3-CX$_3$ benzoic acid structure)	none given	X = H, D, or T	124
XV-46	(indole-3-CD$_2$CN structure)	(indole-3-CD$_2$CD$_2$NH$_2$ structure)	none given	isotopic purity of both starting material and product was 90%	130
XV-47	(2-chlorobenzoic acid structure)	(2-deuteriobenzoic acid structure)	84		123
XV-48[b]	Br—(benzene)—COOH	D—(benzene)—COOH	80		123
XV-49	(2-bromophenoxyacetate Na structure) O—CH$_2$—CO$_2^-$ Na$^+$	(phenoxyacetate, 2-D, Na structure) O—CH$_2$—CO$_2^-$ Na$^+$	36	with sodium carbonate as base	129

TABLE XV (Continued)

reaction no.	starting material	product(s)	yield, %	comments	ref
XV-50			0.79 D atom	m- and p-bromoanilines also gave mostly o-deuterio product	127
XV-51			none given		61
XV-52[b]		CD₃CHDCD(CD₃)COOH	91		125

^{a} An asterisk indicates that the stereochemistry of the material shown was not specified in the original reference, so the stereochemical representation given here is arbitrarily drawn. ^{b} This reaction gave a mixture of isotopomers.

Partial reduction of naphthalenes is achieved with this reagent combination, usually producing the tetrahydro derivatives, and hydrogenation of phenyl groups has been observed under forcing conditions. The reaction generally leads to quantitative extrusion of sulfur and halide atoms. Phenylmercuric acetate has been converted to biphenyl. Isotopic labeling of various substrates has been accomplished by using nickel–aluminum alloy in deuteriated or tritiated aqueous media to effect the required hydrogenation, hydrogenolysis, or exchange reactions.

The procedure compares quite favorably with other reductive methods. It is simple to execute, inexpensive, and unique in its selectivity among various functional groups. Many reductions have been performed by heating in a steam bath, but that does not always appear to be necessary. Reactions can frequently be done by simply stirring at room temperature, though a rapid temperature rise can occur after an induction period. By generating both a dissolving-metal reducing system and catalytic hydrogenation conditions from well-defined starting materials in situ in the presence of the material to be transformed, one can achieve excellent reproducibility of outcome. Rearrangements and other skeletal alterations are seldom encountered, and various strategies have been introduced for suppressing unwanted side reactions and optimizing yields of desired products.

Our goal in publishing this review is to encourage further research with this valuable reducing agent. In particular, we believe work along the following lines would be especially rewarding: (i) fuller exploitation of nickel–aluminum alloy in some of the extremely advantageous applications that are already developed but as yet not widely known; (ii) application to previously untested functional groups; (iii) mechanistic studies aimed at elucidating the relative contributions of catalytic hydrogenation, electron transfer from dissolving aluminum, and solvolysis to the results of various transformations; (iv) determination of the scope and limitations of nickel–aluminum alloy reductions as a means of incorporating hydrogen isotopes and optimization of the conditions for doing so; (v) further development of new or little-used applications, including reductions in aqueous acid; and (vi) other studies aimed at extending knowledge of the reaction's scope and limitations, including further investigation of its stereochemical course and determination of additional structure–reactivity principles in such transformations

as deacylation of aryl rings, reduction of heterocycles, hydrogenolytic ether cleavage, or the reactions of organomercurials.

It is our experience and belief that reduction with nickel–aluminum alloy will prove to be the method of choice for effecting a wide variety of desired transformations, including many for which other reductants are currently employed.

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