THE CHEMISTRY OF IMINES

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CONTENTS

I. INTRODUCTION

This review covers compounds variously referred to as imines, azomethines, anils, or Schiff bases. These materials can be designated structurally as RR'C=NR''.

The nature of the R groups is limited to alkyl or aryl substituents or hydrogen at the point of attachment to the imino (C=N) carbon or nitrogen. No effort has been made to cover imines where R is a group which does not contain carbon at the point of attachment, nor compounds containing the imino group as an integral part of a heterocyclic system, nor ketenimines, $R_2C{=}C{=}NR$. However, R and R' may form a cyclic saturated system. Unsaturated cyclic systems, as benzoquinonimine, are not covered. Sprung's review (254) should be consulted for the chemistry of formaldehyde with amines. This would cover the case where R and R' are hydrogens.

The nomenclature for compounds of this type is often variable. Recently, *Chemical Abstracts* covered these materials under the categories imines and Schiff bases. In this review, these materials will be referred to as imines when the class of compound is considered. Aldimines refer to compounds where R is alkyl or aryl and R' is a hydrogen, while ketimines refer to compounds where both R and R' are alkyl or aryl. For convenience, it is felt that the term Schiff base should be limited to designating only those imines where R is an aryl group, R' is a hydrogen, and R'' either an alkyl or aryl group. Anils should be limited to designating imines where R and R' are aliphatic, aromatic, or hydrogen, and R'' is phenyl or a substituted phenyl group. Such a system is followed in this review. In naming specific imines, the nomenclature followed by *Chemical Abstracts* is used. For example, $C_6H_5CH{=}NC_6H_5$ is named N-benzylideneaniline, and

$$CH_3CH_2CH(CH_3)CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}NC_2H_5$$

is named N-2(4-methylheptylidene)ethylamine. In cases where R'' is a hydrogen atom, the compound is given an imine name. For example, $CH_3CH{=}NH$ is named ethylidenimine. Where R'' is an alkyl or aryl group, the amine nomenclature is used.

Since the chemistry of imines has not been covered comprehensively previously (287), this review covers their chemistry from the time of their discovery by Schiff in 1864 through September of 1962 (234).

It is hoped that this review will demonstrate how the chemistry of imines is both similar to that of aldehydes and ketones and at the same time somewhat unique. In light of this, new chemistry of ketones or aldehydes might more quickly be tried on imines, and perhaps imines might be used along with or instead of ketones and aldehydes to investigate many reaction mechanisms.

II. Physical Properties

Certain imines are known to be liquid crystals (98, 280). It is known that these imines are generally substituted N-benzylideneanilines which are capable of allowing themselves to be arranged parallel to each other forming groups which are more or less oriented. Some imines have also been noted to exhibit phototropy and thermotropy. Most of these are N-salicylideneanilines (31, 59).

Ultraviolet and visible spectra of imines depend too much on substituents to give any generalized data on them. However, the Raman spectra of a number of imines have been determined. A number of N-alkylidenealkylamines give rise to a Raman line near 1670 cm.$^{-1}$ (143). Cantarel (39) also finds that imines have a Raman line in the same region and compares their characteristic frequency with those of C=C and C=O and finds it to be closer to the latter.

	$\Delta\nu$, cm.$^{-1}$
C=C	1600–1650
C=N	1650–1670
C=O	1710–1750

The C=N bond distance for several imines has been deduced from the corresponding Raman frequencies by comparison with the C=O distance for several ketones. The average distance for the C=O bond is close to the accepted value of 1.215 Å., so the imines are considered to be perfectly covalent and the bond distance of 1.24 Å. adopted. The N= radius therefore is 0.575 Å., the C= radius is 0.665 Å. (40). Kahovec also shows imines to have Raman frequencies in the range of 1666–1673 cm.$^{-1}$. He observes no depolarization chain frequencies and concludes that the alkyl groups in aldimines probably have the anticonfiguration (138).

The infrared spectra of imines (of the type R_2C=NH) show that all dialkyl ketimines absorb in the region from 6.08 to 6.10 μ for the C=N bond, while the more conjugated diaryl ketimines absorb at higher wave lengths, about 6.24 μ. If the aryl groups are substituted with deactivating groups such as halogen, a decrease in the conjugation results which lowers the wave length of absorption. Similarly aralkyl ketimines generally absorb between that of the dialkyl and diaryl ketimines. The absorption of the ketone from which the imine is derived is slightly lower than the imine. The absorption for the N–H bond occurs from 3.09 to 3.12 μ (211). The C=N stretching frequencies of various N-benzylideneanilines are found to be of medium intensity in the double bond stretching region from 1613–1631 cm.$^{-1}$ (45).

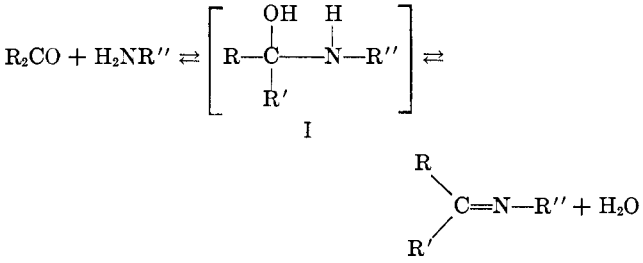
Everard and Sutton report the dipole moment of the C=N bond to be 1.4 *D* for aliphatic aldimines, which is less than the dipole moment of 2.5 *D* for ketones (80). The bond energy of the C=N bond is given as 94 kcal. by Pauling (207), 132 kcal. by Palmer (201), and 139.5 kcal. by Syrkin (266). The molar refractants of the C=N group is given as 1.26 by von Auwers (7).

The following tables are included to give some idea of the physical properties and types of various imines that are known. The tables are not meant to be a complete abstract of all known imines as there are too many. To find any given imine in *Chemical Abstracts*, say N-benzylideneaniline, the parent amine is found—aniline—and then the aldehydic or ketonic portion—N-benzylidene—is sought.

III. Preparation of Imines

A. Reaction of Aldehydes and Ketones with Amines

Perhaps the most common method for preparing imines is the reaction of aldehydes and ketones with amines. This reaction was first discovered by Schiff (234) and imines are often referred to as Schiff bases.

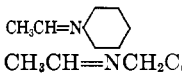
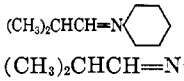
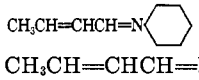


The reaction is acid-catalyzed and is generally carried out by refluxing the carbonyl compound and amine, with an azeotroping agent if necessary, and separating the water as formed.

Most of the work that has been carried out in order to understand the mechanism of this reaction has been done using hydroxylamine or semicarbazide as the amine. Oximes and semicarbazones are not covered in this review but their formation should be analogous to imine formation. Hammett (104) proposes that acids protonate the carbonyl group to give a carbonium ion which adds to the amine in a very fast reaction. The rate-determining step then is the deprotonation of this intermediate to give a carbinolamine I, an

TABLE I

ALKYLCH=NALKYL

Compound	B.p. (mm.)	Yield, %	Ref.
$CH_3CH{=}NCH_3$	27	55	272
$CH_3CH{=}NC_2H_5$	48	77	272
$CH_3CH{=}NC_3H_7$	74	69	272
$CH_3CH{=}NC_3H_7$-*i*	59	69	272
$CH_3CH{=}NC_4H_9$	102	70	272
	54 (18)	76	272
$CH_3CH{=}NCH_2C_6H_5$	94 (21)	18	272
$CH_3CH_2CH{=}NCH_3$	53	77	272
$CH_3CH_2CH{=}NC_2H_5$	74	81	272
$CH_3CH_2CH{=}NC_3H_7$	101	78	272
$CH_3CH_2CH{=}NC_4H_9$-*sec*	111	75	272
$CH_3CH_2CH{=}NC_4H_9$-*i*	144	78	272
$CH_3CH_2CH{=}NCH_2CH{=}CH_2$	102	48	272
$CH_3CH_2CH_2CH{=}NCH_3$	81	76	272
$CH_3CH_2CH_2CH{=}NC_2H_5$	102	84	272
$CH_3CH_2CH_2CH{=}NC_3H_7$	125	78	272
$CH_3CH_2CH_2CH{=}NC_3H_7$-*i*	112	82	272
$CH_3CH_2CH_2CH{=}NC_4H_9$-*i*	166	74	272
$CH_3CH_2CH_2CH{=}NCH_2CH{=}CH_2$	128	66	272
$CH_3CH_2CH_2CH{=}NCH_2C_6H_5$	101 (16)	40	272
$CH_3CH_2CH_2CH{=}NC(CH_3)_2C(CH_3)_3$	60 (2.5)	93	272
$(CH_3)_2CHCH{=}NCH_3$	70	82	272
$(CH_3)_2CHCH{=}NC_2H_5$	90	80	272
$(CH_3)_2CHCH{=}NC_3H_7$	115	77	272
$(CH_3)_2CHCH{=}NC_4H_9$-*sec*	124	79	272
	82 (26)	87	272
$(CH_3)_2CHCH{=}NCH_2C_6H_5$	105 (15)	85	272
$(CH_3)_2CHCH{=}NCH_2CH{=}CH_2$	117	82	272
$(CH_3)_2CHCH_2CH{=}NC_3H_7$	130–139	64	272
$(CH_3)_2CHCH_2CH{=}NC_4H_9$	93 (100)	67	272
$C_6H_{13}CH{=}NCH_3$	160	66	272
$C_6H_{13}CH{=}NC_2H_5$	175	70	272
$C_6H_{13}CH{=}NC_3H_7$	195	66	272
$C_6H_{13}CH{=}NCH_2CH{=}CH_2$	86 (20)	61	272
$C_7H_{15}CH{=}NC_2H_5$	89 (20)	60	272
$C_8H_{17}CH{=}NCH_3$	94 (22)		272
$C_9H_{19}CH{=}NCH_3$	103 (15)	60	272
$CH_3CH{=}CHCH{=}NCH_3$	114	24	272
$CH_3CH{=}CHCH{=}NC_3H_7$	137	23	272
$CH_3CH{=}CHCH{=}NC_3H_7$-*i*	128	65	272
$CH_3CH{=}CHCH{=}NCH_2CH{=}CH_2$	140	32	272
	64–77 (4)	29	
$CH_3CH{=}CHCH{=}NC(CH_3)_2C(CH_3)_3$	108–111	89	126
$CH_3CH_2CH_2CH{=}C(C_2H_5)CH{=}NC(CH_3)_2C(CH_3)_3$	141–148 (17)		126
$(CH_3)_3CCH_2CH(CH_3)CH_2CH{=}NC(CH_3)_2C(CH_3)_3$	80–94 (0.2)	82	126
$[CH_3CH_2CH_2C(CH_3)_2N{=}CH_2{-}]_2$	90 (1)		126
$[C_6H_5C(CH_3)_2N{=}CH_2{-}]_2$	180–200 (1)		126
$[(CH_3)_3CN{=}CH_2{-}]_2$	90–100 (25)		126
$(CH_3)_3CCH{=}NCH_2C(CH_3)_3$	90 (104)	68	186

unstable intermediate, which rapidly eliminates water to give the semicarbazone. More recently Jencks (132) has cogently shown that the carbonyl and amine react rapidly to give the carbinolamine I. This then is dehydrated to the semicarbazone in the rate-determining step which is acid-catalyzed. Only a little work has been done regarding the reaction mechanism where the water is removed by refluxing, as is usually the case in the synthesis of imines. In the reaction of benzaldehyde, aniline, and acid catalyst in benzene containing tributylamine, it has been shown that the reaction is first order with respect to the aldehyde, amine, and catalyst (218). *para*-Substitution of the benzaldehyde with electron-donating groups decreases the reaction rate, while the reverse is true for similarly *para*-substituted anilines. This work agrees with both the Hammett and Jencks mechanisms and more work will be necessary to establish the exact mechanism.

TABLE II

(ALKYL)$_2$C=NALKYL

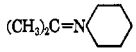
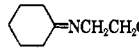
Compound	B.p. (mm.)	Yield, %	Ref.
$(CH_3)_2C{=}NC_3H_7$	107	84	157
$(CH_3)_2C{=}NCH_2CH{=}CH_2$	113	70	157
$(CH_3)_2C{=}NC_4H_9$-*sec*	116	97	157
$(CH_3)_2C{=}NCH_2CH(CH_3)_2$	122	85	157
	181	95	157
$CH_3CH_2(CH_3)C{=}NC_3H_7$	129	96	157
$CH_3CH_2(CH_3)C{=}NCH_2CH{=}CH_2$	135	86	157
$CH_3CH_2(CH_3)C{=}NC_4H_9$-*sec*	134	86	157
$(CH_3)_2CHCH_2(CH_3)C{=}NC_3H_7$	163	88	157
$(CH_3)_2CHCH_2(CH_3)C{=}NCH_2CH{=}CH_2$	110 (100)	99	157
$(CH_3)_2CHCH_2(CH_3)C{=}NC_4H_9$-*sec*	109	96	157
$(CH_3)_2CHCH_2(CH_3)C{=}NC_4H_9$-*i*	175	96	157
$[(CH_3)_2CHCH_2]_2C{=}NC_3H_7$	134 (100)	81	157
$[(CH_3)_2CHCH_2]_2C{=}NC_3H_7$-*i*	126 (100)	62	157
$[(CH_3)_2CHCH_2]_2C{=}NC_4H_9$-*sec*	145 (100)	75	157
$CH_3CH_2CH_2(CH_3)C{=}NCH(CH_3)CH_2CH(CH_3)_2$	110 (50)		110
$CH_3CH_2CH_2CH_2CH_2(CH_3)C{=}NCH_2CH_2OH$	88 (6.5)		110
$[(CH_3)_2CHCH_2]_2C{=}NCH_2CH_2OH$	93 (60)		110
	109 (50)		110

TABLE III

ARYLCH=NARYL

Compound	B.p. (mm.)	M.p.	Ref.
$C_6H_5CH{=}NC_6H_5$			108
$C_6H_5CH{=}NC_6H_4CH_3$-*p*		33–35	108
$C_6H_5CH{=}NC_6H_4Cl$-*p*		56–58	108
$C_6H_5CH{=}NC_6H_4Br$-*p*		66–67	108
$C_6H_5CH{=}NC_6H_4Cl$-*o*	325		159
$C_6H_5CH{=}NC_6H_4CH_3$-*m*	315 (775)		159
$C_6H_5CH{=}NC_6H_4CH_3$-*o*	307 (775)		159
o-$HOC_6H_4CH{=}NC_6H_4Br$-*p*		112	108
p-$CH_3OC_6H_4CH{=}NC_6H_4OCH_3$-*p*		142	108
p-$ClC_6H_4CH{=}NC_6H_5$		66	108
p-$HOC_6H_4CH{=}NC_6H_5$		51	108
$(CH_3)_3C_6H_2CH{=}NC_6H_5$		56	108
$(CH_3)_3C_6H_2CH{=}NC_6H_4Cl$-*p*		74	108
p-$ClC_6H_4CH{=}NC_6H_4Cl$-*p*		111	108
o-$ClC_6H_4CH{=}NC_6H_4Cl$-*p*		68	108
m-$NO_2C_6H_4CH{=}NC_6H_4Cl$-*p*		84	108
p-$NO_2C_6H_4CH{=}NC_6H_4Cl$-*p*		128	108

TABLE IV

RR'C=NH R and R' are alkyl or aryl

Compound		B.p. (mm.)	M.p.	Yield, %	Ref.
R	R'				
2-Cyclohexylethyl	*sec*-Butyl	101 (2)		56	212
2-Cyclohexylpropyl	*sec*-Butyl	107 (1)		43	212
2-Cyclohexylbutyl	*sec*-Butyl	121 (1)		45	212
2-Cyclohexylpentyl	*sec*-Butyl	130 (1)		60	212
m-Tolyl	Isopropyl	227 (740)			211
p-Tolyl	Isopropyl	228 (740)			211
o-Tolyl	*t*-Butyl	235 (740)			211
m-Tolyl	*t*-Butyl	238 (740)			211
p-Tolyl	*t*-Butyl	235 (740)			211
Phenyl	Ethyl	101 (13)			189
Phenyl	Propyl	99 (8)			189
Phenyl	Isobutyl	113 (12)			189
Phenyl	Cyclohexyl	136 (5)			189
Phenyl	Phenyl	127 (3)			189
Phenyl	*o*-Tolyl	136 (4)			189
Phenyl	*p*-Tolyl	147 (5)	37		189
Phenyl	α-Naphthyl	182 (4)	68–69		189

TABLE V

ALKYLCH=NARYL

Compound	B.p. (mm.)	M.p.	Ref.
$CH_3CH_2CH{=}NC_6H_5$		103.4	183
$CH_3CH_2CH_2CH{=}NC_6H_5$			183
$(CH_3)_2CH{=}NC_6H_5$		140	183
$CH_3CH_2CH_2CH_2CH{=}NC_6H_5$		97	183
$(CH_3)_2CHCH_2CH{=}NC_6H_4CH_3$-*p*		99	183

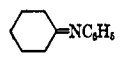
TABLE VI

CYCLIC ALIPHATIC KETONE ANIL

Compound	B.p. (mm.)	M.p.	Ref.
Cyclohexanone anil	140 (19)		224
Methone anil	160 (12)		224
Dihydrocarvone anil	170 (15)		224
Pulegone anil	142 (12)		224
Carvone anil	181 (17)		224
Camphor anil		13.5	224
2-Cyclohexylidene cyclohexanone anil	210 (14)		224
Methone cyclohexanone (*p*-toluidine)	178 (16)		224
Methone cyclohexanone (*p*-anisidine)		62	224

TABLE VII

(ALKYL)(ALKYL OR ARYL)C=NARYL

Compound	B.p. (mm)	M.p.	Yield, %	Ref.
$(CH_3)_2C{=}NC_6H_5$	86 (13)	23.5		244,322
$(C_2H_5)_2C{=}NC_6H_5$	117 (25)		75	120
$(C_3H_7)_2C{=}NC_6H_5$	130 (17)		76	120
$(C_3H_7)_2C{=}NC_6H_4CH_3$-*o*	140 (18)		84	120
$(C_3H_7)_2C{=}NC_6H_4CH_3$-*m*	144 (20)		74	120
$(C_3H_7)_2C{=}NC_6H_4CH_3$-*p*	144 (17)		63	120
$C_9H_{19}(CH_3)C{=}NC_6H_5$	206 (24)		60	120
	157 (30)		65	120
$C_6H_5(CH_3)C{=}NC_6H_5$	175 (13)			227
$C_6H_5(CH_3)C{=}CHC(C_6H_5){=}NC_6H_5$	250 (13)	98–99		227
$(C_6H_5)_2C{=}NC_6H_5$		113		227
$(C_6H_5)_2C{=}NC_6H_4CH_3$-*p*	225 (15)			227
$(C_6H_5)_2C{=}NC_{10}H_7$-α		138		227
$C_6H_5C(\alpha\text{-}C_{10}H_7){=}NC_6H_5$		94		227

Primary aliphatic aldehydes, in general, give polymeric materials with amines. This is due to the ease with which the imine initially formed undergoes subsequent aldol condensations. For example

$$X(RCH_2CH{=}NR) \rightarrow CH_2CH(=\overset{R}{C}CH=)_zCCH{=}NR$$

Amines, containing an attached tertiary alkyl group, are reported to give imines with primary aldehydes possibly because steric hindrance makes aldol condensations difficult (126). It has also been shown that by slowly adding a primary aldehyde to an aliphatic amine at 0° followed by an addition of potassium hydroxide, separation of the organic material from the water, and distillation from potassium hydroxide that imines of this type can be obtained in fair yields (38). Tiollais had previously obtained imines of this type in a similar manner (272).

The dimeric form of N-butylideneaniline $C_6H_5N{=}CHCH(CH_2CH_3)CH(NHC_6H_5)CH_2CH_2CH_3$ has been isolated (141, 183). This material can readily deaminate on heating or in the presence of acids to give the α,β-unsaturated imine and consequently is formed at room temperature or lower. Other aldehydes are also reported to give similar dimers. Aliphatic amines and aldehydes have not been reported to give dimers. Similarly aliphatic ketones have not given dimers.

Secondary aliphatic aldehydes readily form imines with amines (183). The fact that these aldehydes have only one α-hydrogen makes their imines incapable of splitting out amine to give an α,β-unsaturated imine which would result in polymerization.

Tertiary aliphatic and aromatic aldehydes react readily and nearly quantitatively with amines to give the corresponding imines even at room temperature. Aromatic aldehydes are so reactive that imines form quantitatively even without the removal of the water formed during the reaction (234). Sprung has reviewed the chemistry of aldehydes with amines (254). Imine formation as well as other reactions are covered. Of special interest here may be the chemistry of formaldehyde and amines since no imine is formed from formaldehyde.

Aliphatic ketones react with amines more slowly than aldehydes to form imines. This necessitates the use of higher reaction temperatures and longer reaction times than required for the aldehydes. Acidic catalysts are helpful and water removal from the reaction mixture is definitely required. Fairly high yields of imines can be obtained in this way (80–95%).

The structure of the ketone is important in understanding how much aldol condensation product will be obtained and how fast the imine will form. Sterically hindered ketones react more slowly than unhindered ones and Newman's rule of six can be applied to roughly estimate the reactivity of ketones with amines (194). For example, diisobutyl ketone takes much longer to react with aniline than does 2-heptanone (54).

Aldol condensation products form more readily from methyl ketones than from methylene ketones. Strong acids are suitable catalysts for methylene ketone reactions while their use should be avoided for methyl ketone reactions. For methyl ketones, weak acid catalysis seems to be quite effective, and a weak acid salt of a weak acid catalyst system assures the best results (160). For low boiling ketones, such as acetone and methyl ethyl ketone, where reaction times would be long, one can use Kuhn's method where silver iodide and aniline hydriodide in dimethylformamide when gradually treated with acetone and then with sodium hydroxide and potassium cyanide give a 90% yield of N-isopropylideneaniline (154).

Aromatic ketones react even slower than aliphatic ketones with amines. Here proton and Lewis acid catalysts are required as well as high reaction temperatures. Acetophenone and benzophenone react with aniline at reflux temperatures in the presence of aniline hydrochloride or aniline zinc chloride salt to give the imines (227). Ammonia also reacts with these ketones at 180° in 4 hr. with an aluminum chloride catalyst (264). A vapor phase reaction of these ketones with ammonia over thorium oxide at 300–400° is also useful (178). Hydrogen cyanide catalyzes the reaction of acetophenone with aniline. It also adds to the imine as formed to give an α-cyanoamine which can be dehydrocyanated at 210° to give the imine (70).

Concerning the amine used in the reaction, it can be said that the weaker the amine the slower will be its reaction rate with any given carbonyl compound.

Ammonia reacts uniquely with aldehydes and ketones. For example secondary aldehydes, as isobutyraldehyde, and ammonia gives N,N′-diisobutylidene-1,1-isobutyldiamine (109). This when distilled slowly eliminates ammonia and gives N-isobutylideneisobutylamine in 95% yield.

$$(CH_3)_2CHCHO + NH_3 \rightarrow [(CH_3)_2CHCH{=}N]_2CHCH(CH_3)_2 \rightarrow (CH_3)_2CHCH{=}NCH_2CH(CH_3)_2 + NH_3$$

Similarly tertiary aldehydes, as neopentaldehyde, and ammonia gives N-neopentylideneneopentylamine and *t*-butyl cyanide in 80% yield.

$$(CH_3)_3CCHO + NH_3 \rightarrow [(CH_3)_3CCH{=}N]_2CHC(CH_3)_2 \rightarrow (CH_3)_3CCH{=}NCH_2C(CH_3)_3 + (CH_3)_3CCN$$

B. REACTION OF NITRILES WITH ORGANOMETALLIC COMPOUNDS

Moureau and Mignonac (189) were the first to add an aryl or alkyl Grignard to an aryl cyanide to obtain, after careful hydrolysis at −15°, treatment with hydrogen chloride, and finally with ammonia, the ketimine in 70% yield.

$$PhCN + PhMgBr \rightarrow PhC(=NMgBr)Ph \xrightarrow[H^+]{H_2O} PhC_2{=}NH$$

It should be remembered that the hydrolysis of the organometallic intermediate to the ketimine unless carefully carried out can be followed by further hydrolysis to the ketone.

2,2,6-Trimethylcyclohexyl cyanide and phenylmagnesium bromide give a ketimine which is rather stable toward hydrolysis (166). *t*-Butyl *o*-tolyl ketimine was also found to be stable toward hydrolysis (213). These demonstrate the steric stabilization of certain imines to hydrolysis and probably other addition reactions although these have not been investigated. Pickard (214) was the first to report the reaction of an aliphatic cyanide with an aliphatic Grignard. He also found that very high yields of ketimine could be obtained when the cyanide–Grignard complex is slowly decomposed with anhydrous methanol rather than with anhydrous ammonia or aqueous decompositions (212).

2-Picolyllithium gives imines (after hydrolysis) when it is added to an aryl or alkyl cyanide (218).

C. REACTION OF CARBON–NITROGEN DOUBLE BOND COMPOUNDS WITH ORGANOMETALLICS

Busch (34, 35) found that the chlorine atom in C-chloro-N-benzylideneanilines could be replaced by the alkyl or aryl groups of a Grignard reagent in very good yields to give the corresponding imines.

$$PhC(Cl){=}NAr + RMgX \rightarrow PhC(R){=}NAr$$

Montagne (185) later found that anilides, which may be regarded as C-hydroxyimines, react with alkyl or aryl Grignards to give the corresponding imine in about 40% yield.

$$EtMgBr + PrCONHPh \rightarrow PrC(Et){=}NPh$$

Grammatickis (97) has also found that oximes of aromatic aldehydes react with Grignards to give as the predominant product the benzylamine of the Grignard with the ketimine as the secondary product.

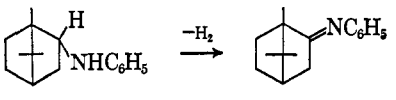
$$ArCH{=}NOH + RMgX \rightarrow ArCHNHR + ArC(R){=}NH$$

The slow addition of Grignards to N-chloroimines in ether gives the nitrile in 20% and the imine in 50% yield (162).

$$R_2C{=}NCl + R'MgX \rightarrow RCN + R_2C{=}NR' + RCl + MgX_2$$

D. DEHYDROGENATION OF AMINES

Ritter (231) was the first to dehydrogenate amines to give imines. He found that isobornylaniline is readily dehydrogenated with sulfur at 220° to give an 89% yield of the anil of camphor.



Later it was found that this method is also effective for dehydrogenating benzhydrylamine, N,N′-diiospropylaniline, and N-α-phenylpropylaniline. Isobornylaniline is also dehydrogenated with amyl disulfide (232). Isobornyl acetanilide and sulfur gives the anil of camphor. Numerous side reactions, such as addition of hydrogen sulfide to the imine, reduction of the imine, and others, occur under these reaction conditions. Selenium is also reported to dehydrogenate amines to imines (36).

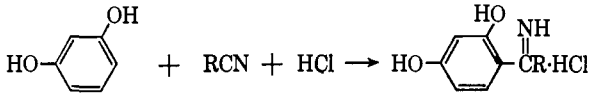
Catalytic dehydrogenation of secondary amines over nickel, platinum, or chromium catalysts at 180° gives the imines (12, 110), but more work in this area would be useful.

Secondary amines, which are prepared from phenols, hexamethylenetetramine, and 2-ethoxyethanol, are readily dehydrogenated to the imine by heating with hexamethylenetetramine in acetic acid (72).

$$(HOC_6H_4CH_2)_2NH \rightarrow HOC_6H_4CH_2N{=}CHC_6H_4OH$$

E. REACTION OF PHENOLS AND PHENOL ETHERS WITH NITRILES

Hoesch and Houben (121, 122, 124) found that phenols or their ethers react with alkyl or aryl cyanides in ether when catalyzed by hydrogen chloride and or zinc chloride to give ketimines in very good yields. The reaction works readily for dihydroxy compounds or monoethers where the groups are *meta* to one another. The reaction is carried out by dissolving the phenol and nitrile in ether and saturating the solution with hydrogen chloride. In the case of less reactive phenols, zinc chloride is also added.



F. REDUCTION OF CARBON–NITROGEN COMPOUNDS

Oximes of aliphatic and aromatic ketones can be reduced with hydrogen and nickel under pressure to give ketimines. Acetophenone oxime gives the imine in 30% yield (179).

$$R_2C{=}NOH + H_2 \rightarrow R_2C{=}NH + H_2O$$

Nitriles when hydrogenated over nickel or platinum catalysts can give imines, but generally the yields are poor due to a further reduction to the amine and to condensations (101).

$$RC{\equiv}N + H_2 \rightarrow RCH{=}NH + H_2 \rightarrow RCH_2NH_2$$

$$RCH{=}NH + RCH_2NH_2 \rightarrow RCH_2NHCH_2R + NH_3$$

Lithium aluminum hydride in tetrahydrofuran has been found to reduce aromatic nitriles to give amines and to give an imine which is formed from the addition of the amine to the nonisolable imine intermediate followed by an elimination of ammonia. This is similar to the above catalytic hydrogenation of nitriles (251).

$$PhCN \xrightarrow{LiAlH_4} PhCH_2NH_2\ (50\%) + PhCH_2N{=}CHPh\ (30\%) + NH_3$$

Nitriles also can be reduced to imines with stannous chloride in ethyl acetate containing hydrogen chloride (261). The imines are isolated as the stannic chloride salt.

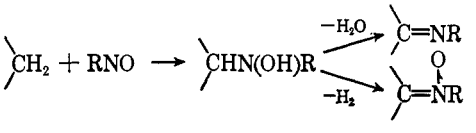
α-Nitrostyrenes can be reduced with lithium aluminum hydride below 0 then hydrolyzed with 20% aqueous potassium sodium tartrate to give the imine (96).

$$PhCH{=}CHNO_2 \rightarrow PhCH_2CH{=}NH$$

G. REACTION OF NITROSO COMPOUNDS WITH ACTIVE HYDROGEN COMPOUNDS

Early workers reported the reaction of active hydrogen compounds with nitroso compounds formed imines. Later workers, however, showed that nitrones were the reaction products rather than the expected imines. More recently it has been found that certain active hydrogen compounds do give imines rather than nitrones so that both materials are formed (15, 209).

An understanding of just what favors nitrone formation or what favors imine formation in this reaction is not presently known with clarity, although some work has been done to investigate this point. The reactions can be pictured as



Azzam (9), in the reaction of benzyl cyanide and *p*-nitroso-N,N-dimethylaniline, has found that imine formation is favored when a strongly basic catalyst, such as sodium hydroxide, and high reaction temperatures are used. The nitrone is favored when a weak base, as piperidine, is used as the catalyst.

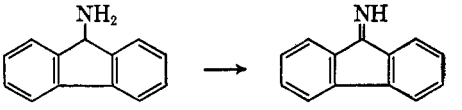
Krohnke (152) has more recently studied the reaction of 2- and 4-picoline methiodide and *p*-nitroso-N,N-diethylaniline. He has found that a ration of two moles of nitroso compound to one mole of picoline methiodide gives the highest yield of crude product when catalyzed with 2 *N* sodium hydroxide. However, the imine to nitrone ratio is higher when the reactant ratio is one to one. It appears that more clarification of this reaction is needed.

H. REACTION OF METAL AMIDES

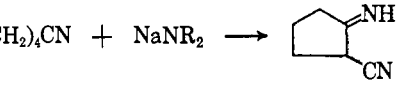
An alkali metal or calcium salt of primary amines reacts with aromatic ketones to give imines (32).

$$(C_6H_5)_2C{=}O + C_6H_5NHNa \rightarrow (C_6H_5)_2C{=}NC_6H_5$$

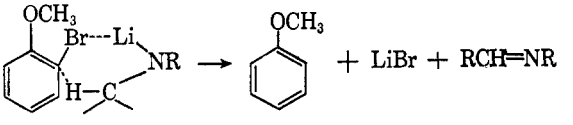
Hauser (114) allowed 9-aminofluorene and potassium amide to react in ammonia to give the imine in 50% yield. In the same way, benzhydrylamine gives a low yield; however, when benzhydryl chloride is added, the yield is raised to 78%.



The alkali, calcium, magnesium, or aluminum metal amide of a secondary amine in ether reacts with dinitriles, as adiponitrile, to give the cyclic α-cyanoimine (286).



Mosher (186) has shown that Benkeser's (19) hypothesis that 2-bromoanisole reacts with the lithium amide of a secondary amine containing an α-hydrogen to give an imine is correct. He finds that N-2,2-dimethylpropylidene-2′,2′-dimethylpropylamine, a very stable imine, is formed when lithium diisobutylamide reacts with 2-bromoanisole. The following cyclic mechanism is proposed.



Less stable imines cannot be prepared in this manner.

I. MISCELLANEOUS METHODS

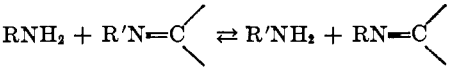
Diethyl ketals when refluxed with alkyl- and arylamines give imines (42, 120). Very good yields are obtained with aromatic amines while aliphatic amines give poorer yields.

$$(C_2H_5O)_2C(CH_3)C_6H_5 + H_2NC_6H_5 \rightarrow CH_3(C_6H_5)C{=}NC_6H_5 + 2C_2H_5OH$$

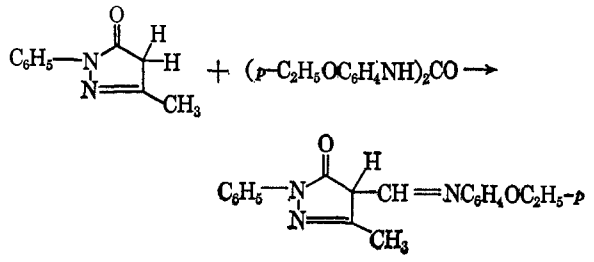
Tertiary alkyl or aryl nitriles react with sodium in petroleum ether to give the di-*t*-alkyl or aryl ketimines in good yield (107).

$$R_3CCN + Na \rightarrow (R_3C)_2C{=}NNa \xrightarrow{H^+} (R_3C)_2C{=}NH$$

Imines react with other amines to give the exchange products. In cases where the added amine is higher boiling than the amine of the imine, a good yield of the exchanged product can be obtained by distilling off the low-boiling amine (111, 226).



Barbituric acid reacts with diphenethylformamidine in refluxing dioxane to give the imine in good yield (205).



Nitrones react with potassium cyanide to give C-cyanoimines (18).

$$C_6H_5CH{=}N(O)C_6H_5 + KCN \rightarrow C_6H_5C(CN){=}NC_6H_5$$

Ethyl N-phenylformimidate, when heated with polycyclic phenols, gives the imine; thus, β-naphthol at 150° gives 2-hydroxy-1-naphthylideneaniline. The ethyl N-phenylformimidate can be formed *in situ* from ethyl orthoformate, aniline, and diphenylformamidine (147).

Phenyl isocyanate and *p*-dimethylaminobenzaldehyde at 190° form the imine in nearly quantitative yield.

$$C_6H_5NCO + p\text{-}(CH_3)_2NC_6H_4CHO \rightarrow p\text{-}(CH_3)_2NC_6H_4CH{=}NC_6H_5 + CO_2$$

Similarly phenyl isocyanate and bis-(*p*-dimethylaminophenyl)thioketone gives the same product with COS liberation (259).

N-Benzylidene and N-cinnamylidenechloroimines are thermally decomposed at 120 to 210° to give nitriles in 90% yield. The imines are formed as a by-product in about 5% yield (115).

Olefins react with hydrazoic acid in sulfuric acid to give imines (1).

$$RR'C{=}CHR'' + HN_3 + H_2SO_4 \rightarrow RR'C{=}NCH_2R'' + N_2$$

Similarly tertiary alcohols or halides react with hydrazoic acid in sulfuric acid to give imines. Benzhydrol under the same conditions gives N-benzylideneaniline in 90% yield (28).

Imines are formed as a by product in the Hofmann rearrangement of benzhydrylacetamide (223).

Phenyl isocyanate and α-thiylbenzylaniline, when heated at 90° in ligroin, give a mixture of products among which are N-benzylideneaniline (255).

Oximes or the benzoyl derivatives of α-amino ketones (containing two α-hydrogens) solvolyze, when in the *anti* form, to give the imine and nitrile (86).

$$(CH_3)_2NCH_2C(C_6H_5){=}NOC(O)C_6H_5 \rightarrow (CH_3)_2N{=}CH_2 + C_6H_5CN + C_6H_5CO_2H$$

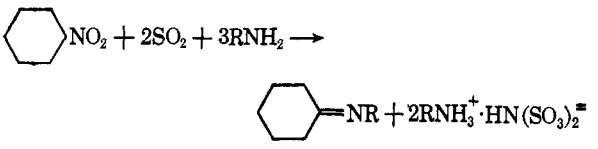
Hydroperoxides and peroxides have recently been shown to oxidize primary and secondary aliphatic amines to imines. Thus *t*-butyl hydroperoxide and 4-methyl-2-pentylamine gives 2-(4-methylpentylidene)-4-methyl-2-pentylamine in 66% yield. *t*-Butyl alcohol and water form from the peroxide. Di-*t*-butyl peroxide reacts similarly (60).

$$RNHCHR'R'' + R'''OOH \rightarrow RN{=}CR'R'' + R'''OH + H_2O$$

In electron paramagnetic resonance studies of the reaction of *t*-butyl hydroperoxides with alkylamines a free radical intermediate RR'CHNOCHR'R has been detected and a reaction mechanism proposed (48).

The Guerbet reaction when applied to amines gives imines as the main product but in low yields. Thus *n*-hexylamine, potassium phosphate, and a copper chromite–nickel (1:1) catalyst when refluxed 24 hr. gives N-hexylidene-*n*-hexylamine in 13% yield (181).

Secondary nitroalkanes react with primary amines in petroleum ether at 60° to give primarily bis-(cyclohexylamino)imidodisulfonate but some imine is also formed (279).



Urea and cyclohexanone in refluxing triethylamine gives N-cyclohexylidene-2-carbamylcyclohex-1-enylamine in 28% yield (176).

Alkylidenetriphenylphosphoranes react with nitrosobenzene to give anils (240).

$$RR'C{=}P(C_6H_5)_3 + ONC_6H_5 \rightarrow RR'C{=}NC_6H_5 + OP(C_6H_5)_3$$

1-Butylperfluoroisobutylene reacts with ethylamine in ether to give N-2-[(1-bis-trifluoromethyl)hexylidene]-ethylamine in 26% yield (148).

$$(CF_3)_2C{=}CHC_4H_9 + C_2H_5NH_2 \rightarrow (CF_3)_2CHC(=NC_2H_5)C_4H_9$$

Ketones, as well as amines as previously noted can react with ketimines to exchange the higher for the lower boiling ketone (112). The reaction is acid-catalyzed. For example, N-*sec*-butylidene-2-(4-methylpentyl)-amine and 4-methyl-2-pentanone react in the presence of an acid. The methyl ethyl ketone is removed as formed by distillation to give the exchanged imine. This reaction is especially suitable for preparing α,β-unsaturated imines, since the unsaturated aldehydes, as crotonaldehyde or α-methylacrolein, give 1,3-diaminopropanes by a 1,4-addition on direct reaction with amines instead of the desired imines (246).

Lithium *t*-butylamide in ether and benzene when slowly treated with 3-chloro-4-methylbutyne-1 give N-2-methylbuten-2-ylidene-*t*-butylamine (73).

$$(CH_3)_2C(Cl)C{\equiv}CH + LiNHC(CH_3)_3 \rightarrow (CH_3)_2C{=}CH{-}CH{=}NC(CH_3)_3 + LiCl$$

α-Amino acids react with sodium hypochlorite to give the chloramine intermediate which decomposes with the elimination of carbon dioxide and sodium chloride to give the imine (157).

$$RR'(NHR'')CO_2H + NaClO \rightarrow RR'C(NClR'')CO_2Na \rightarrow RR'C{=}NR'' + CO_2 + NaCl$$

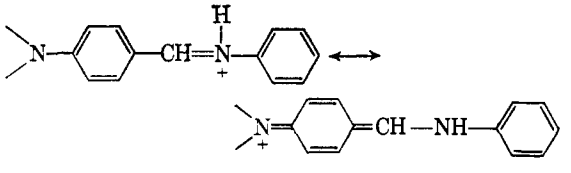
The reaction of acetylene at 200 p.s.i. with primary aliphatic amines in the presence of zinc and cadmium acetates at 140° for 20 hr. yields N-ethylidenealkylamines in about 55% yields. Higher α,β-unsaturated imines are also formed due to aldol condensations of the imine (153).

IV. Addition Reactions of Imines

A. ADDITION OF WATER

It can be recalled that all stages in the preparation of imines from carbonyl compounds and amines are reversible. Consequently, hydrolysis of imines to the starting components is possible. Reddelien and Danilof (228) have reported that anils are readily decomposed by aqueous mineral acids, but that they are stable towards aqueous base. Alumina and thoria have also been found to be effective catalysts for the hydrolysis of imines (170).

Substituents on the benzylidene portion of N-benzylideneaniline have been found to facilitate hydrolysis when they are electron-donating while the electron-withdrawing groups retard hydrolysis. For example N-*o*- and *p*-methoxybenzylideneanilines hydrolyze faster than N-benzylideneaniline itself which hydrolyzes faster than N-*o*-, *m*-, or *p*-nitrobenzylideneanilines (158). Similarly phenyl furyl ketimine hydrochloride hydrolyzes more slowly than diphenyl ketimine hydrochloride, which is in agreement with a commonly observed rule that ketimine salts with more negative groups attached to the carbon of the imino group are more resistant to hydrolysis than those containing more electron-donating groups (52). Aliphatic ketimines are hydrolyzed more rapidly than aromatic ketimines. An exception to this rule is the hydrolysis of N-4-dimethylaminobenzylideneaniline. This material hydrolyzes more slowly than N-benzylideneaniline in dilute aqueous acid. This is attributed to resonance stabilization (282) of the protonated intermediate.



Steric factors are also important in the rate of hydrolysis. For example, *o*-tolyl phenyl ketimine hydrochloride hydrolyzes much slower than the *meta* or *para* tolyl salts (51). It has previously been mentioned that 2,2,6-trimethylcyclohexyl phenyl ketimine and 1-(*o*-tolyl) neopentyl ketimine are very resistant to hydrolysis (166, 213).

The mechanism of the hydrolysis of imines has always been felt to proceed through the carbinol intermediate I with the acid-catalyzed dehydration of I being the rate-determining step in the reaction. The most recent work in this area (229) indicates that an intermediate forms and decomposes by an uncatalyzed and by an acid-catalyzed reaction path. The intermediate is present throughout the reaction only in a low steady-state concentration.

B. ADDITION OF HYDROGEN

Imines may be reduced either by a catalytic hydrogenation or by chemical reagents.

Catalytic hydrogenations of imines are for the most part avoided when the corresponding amines are desired. In practice a direct reductive alkylation (76) of the carbonyl compound and amine gives a higher yield of product in a more convenient manner. This is especially true in cases where the imine is sensitive to

$$RR'C{=}O + H_2NR'' + H_2 \rightarrow RR'CHNHR'' + H_2O$$

aldol type condensation reactions, as aliphatic aldimines.

Imines can be reduced to the amines if desired. Aliphatic aldimines give the secondary amines in 40–65% yield by a platinum catalytic reduction at 50° (38). Aliphatic ketimines are reduced over platinum catalysts to give rather high yields, 83–93%, of the secondary amine (47, 105). Other catalysts such as nickel at 100° and copper chromite at 200° and about 1000 p.s.i. of hydrogen also reduce imines of this type. Schiff bases, such as N-benzylideneaniline, are reduced in virtually quantitative yields over platinum at 50°, nickel at 100°, and copper chromite at 175° (2).

Imines derived from ammonia ($R_2C{=}NH$) generally undergo addition reactions with the amines produced during the hydrogenation to give poor yields of the desired amine and here again the reductive alkylation route offers the best route to the desired amine. See the preparation of imines by reduction of nitriles.

Vapor phase hydrogenations of imines have also been run. Mailhe (169) reduced N-benzylideneaniline over nickel at 220 to 230°. He also reduced N-isobutylideneethylamine by this method.

N-Benzylideneaniline has also been reduced with cobalt carbonyl, carbon monoxide at 60 atm., and hydrogen at 180 atm. at 135° (193).

There are many chemical reagents which will reduce imines. Most, but not all, of the reagents that are used to reduce ketones and aldehydes will reduce imines. Aqueous systems, especially where acids are present, are not suitable for imine reductions. Sodium and refluxing alcohol (13, 85) reduces imines. Sodium amalgam is also effective. Zinc and acetic acid is reported to be an effective reducing system as is sodium hydrosulfite in basic solution (167). Magnesium in methanol reduces imines (287), but during the reaction heating or cooling may be needed in any given case. Lithium aluminum hydride (41, 188, 252) is an effective reducing agent. Sodium aluminum hydride works in the same way as does the lithium aluminum hydride.

Sodium borohydride (82) in methanol at 0° also works. The imino group can be selectively reduced in the presence of other groups such as nitro, chloro, methoxy, and hydroxyl with sodium borohydride (45, 123). Dialkylaluminum hydride (23) also reduces imines. Dimethylborane (195, 196) has also been found to reduce imines very rapidly at 20° in very good yields. Groups such as chloro, nitro, hydroxyl, methoxy, carbethoxy, and sulfonamido are not reduced (24).

N-Benzylideneaniline is reduced with *p*-thiocresol on refluxing to give the amine and the disulfide (95). Electrolytic reductions of imines to the amines are also possible (159).

Grignard reagents in the presence of cobaltous chloride give N-benzylbutylamine in 98% yield in the reaction with N-benzylidenebutylamine (241).

Imines under certain conditions give bimolecular reduction products analogous to pinacol formation of ketones. Anselmino (5) has found that aluminum amalgam in ether converts N-benzylideneaniline to 1,2-dianilino-1,2-diphenylethane.

$$2C_6H_5CH{=}NC_6H_5 \xrightarrow{Al(Hg)} C_6H_5CH(NHC_6H_5)CH(NHC_6H_5)C_6H_5$$

The usual reagent for the bimolecular reduction of diaryl ketones, a mixture of magnesium and magnesium iodide, is also useful for the bimolecular reduction of imines (269). This reduction proceeds faster and in better yields for the reduction of N-benzylidenearylamines than for N-benzylidenealkylamines. Where halogen, methoxy, and dimethylaminobenzylidene anilines were reduced, the yields were lower than for the parent compound.

N-*o*-Methoxybenzylideneaniline is reduced to 1,2-dianilino-1,2-di-*o*-methoxyphenylethane in 90% yield using sodium and toluene. Both the *meso* and racemic isomers were isolated (130, 131).

Isopropylmagnesium chloride reduces N-benzylidenebutylamine in the presence of manganous chloride to give the bimolecular reduction product in 81% yield (242). The bromide gives a 55% yield, while the iodide gives a 44% yield. Cobaltous chloride causes the imine to be reduced to the amine.

C. ADDITION OF PRIMARY AMINES

Just as water adds to imines so should primary and secondary amines. The intermediate 1,1-diaminoalkane (II) is not stable and in the case of secondary amines no reaction occurs because deamination of the

$$\text{>C=NH} + R'R''NH \rightleftarrows \text{>C(NR'R'')NHR}$$

II

intermediate II can only give the starting materials. In the case of primary amines, intermediate II now has two possible means of deamination and consequently an exchange reaction can occur.

$$\text{>C=NR} + H_2NR' \rightleftarrows \text{>C(NHR')NHR} \rightleftarrows \text{>C=NR'} + H_2NR$$

This exchange reaction was first used by Reddelien (226) to obtain imines. Generally the added amine is higher boiling than the liberated amine. Thus by removal of the lower boiling amine, the desired reaction is favored. The reaction is useful for both aryl and alkyl aldimines and ketimines.

It has also been found that as the basicity of the displacing amine increases, the rate of displacement rises in a nearly linear manner (218). This accounts for the fact that *p*-methoxyaniline can displace *p*-nitroaniline from N-benzylidene-*p*-nitroaniline without removing the amine (217).

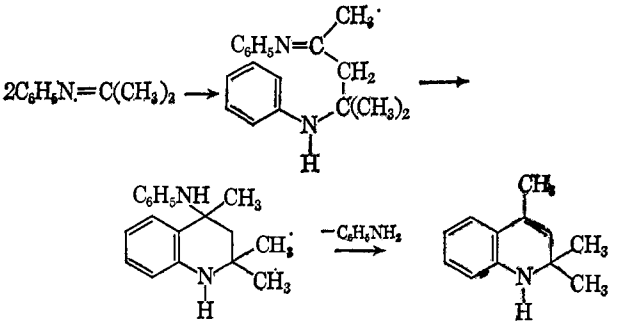
Hydroxylamine also reacts with mesitylethyl ketimine to give the oxime (116). This type of reaction should also be capable of giving semicarbazones, hydrazones, etc., in reactions of imines with amines of the structure H_2NR, where R is a group other than carbon.

D. ADDITION OF ACTIVE HYDROGEN COMPOUNDS

Numerous compounds containing an active hydrogen add to the imines in the following manner

$$RR'C{=}NR'' + R'''H \rightarrow RR'R'''CNHR''$$

Imines derived from aliphatic aldehydes and ketones which contain an α-hydrogen undergo aldol condensations. For example, N-2-propylideneaniline reacts with itself in the presence of hydrogen chloride at about 100° to give 2,2,4-trimethylhydroquinoline. This involves an aldol condensation, cyclization, and deamination (144, 145, 146).



Similarly N-*n*-butylidene-*n*-butylamine when refluxed at 150° for 3 hr. gives a 65% yield of N-2-ethylhexen-2-ylidene-*n*-butylamine (77).

N-Butylideneaniline on standing at room temperature for 24 hr. gives a 78% yield of N-2-ethylhexen-2-ylideneaniline (141).

$$2CH_3CH_2CH_2CH{=}NR \rightarrow CH_3CH_2CH_2CH{=}\overset{\displaystyle CH_2CH_3}{\overset{|}{C}}CH{=}NR + H_2NR$$

Additions of other active hydrogen compounds to aliphatic imines have rarely been reported. This is

probably due to the fact that aldol condensation reactions occur to a greater extent than does the desired addition reaction. Perhaps more work in this area might prove interesting. For example, it has been reported that acetylene adds to N-butylidene-*t*-butylamine in the presence of cuprous chloride at 45° in dioxane to give 3-*t*-butylaminohexyne-3 (177).

$$C_4H_9{=}NC(CH_3)_3 + HC{\equiv}CH \rightarrow CH_3CH_2CH_2\underset{\displaystyle C{\equiv}CH}{\underset{|}{C}}HNHC(CH_3)_3$$

Most of the addition reactions of active hydrogen compounds with imines have been carried out with Schiff bases. These imines have no α-hydrogens and cannot undergo self-aldol condensations.

Some of the active hydrogen materials which have been added to N-benzylideneanilines are: acetoacetic esters and benzoylacetic esters (235), diethyl malonate (174, 235, 278), methyl ethyl ketone (the methyl group adds rather than the methylene) (174), 2-methylbenzopyrrole (active hydrogen is in the 3-position) (203), benzopyrrole (adds in the 3-position) (202), antipyrine (204), α-cyanoethyl acetate, ethylmalonamide, malonamide (161), methyl ketones with boron trifluoride etherate in equimolar amounts (methylene ketones do not react under these conditions) (248), Kojic acid (adds in the 6-position) (14), 2-methylquinoline methyl iodide (139), methyl nitrite, diethylamine favors the addition of ethyl and propyl nitrites (163), isopropyl nitrite fails to react (125), benzyl nitrite adds very easily in the presence of diethylamine (63), α-nitroethyl acetate (65), 8-hydroxyquinoline (adds in the 7-position) (210), α-phenylethyl acetate with an aluminum chloride catalyst (155), benzyl sodium sulfonate with phenyllithium (172), acetophenone with an amine hydrochloride catalyst (149), the sodium salt of phenylacetic acid in sodamide (253), the ethyl ester of phenylacetic acid (155), acetic anhydride (mono product) (4), α- and β-naphthol (22), nitroacetonitrile (230), ethylnitroacetic acid (65, 66) and ω-nitroacetophenone (69). N-Benzylidene-*o*-carboxyaniline exists as an equilibrium of the imine and the cyclic addition product (249).

Concerning reactivity, Philpott and Jones have observed that aldehyde anils are more reactive than ketone anils in the addition reaction of ethylacetoacetic ester.

Other imines which do not possess α-hydrogens are reported to undergo addition reactions with active hydrogen compounds. N-Methylidene-*t*-butylamine reacts with 2,4,5-trichlorophenol in the 6-position (81). N-Benzylidenemethylamine and α-phenylacetic acid react (17).

α-Tolyl ethyl acetate adds to N-benzylideneamines and to β-naphthyl ethyl ketimine (184). N-Furfurylidene and N-benzylidenemethylamines react with α-nitroacetophenone (69).

The amine portion of the imine does not seem to be too important in determining whether or not addition of active hydrogen compounds will occur.

Steric effects, however, should also be important. Except for hydrolysis and addition reactions of Grignard, steric hindrance to other addition reactions have not been mentioned.

E. ADDITION OF ORGANOMETALLICS

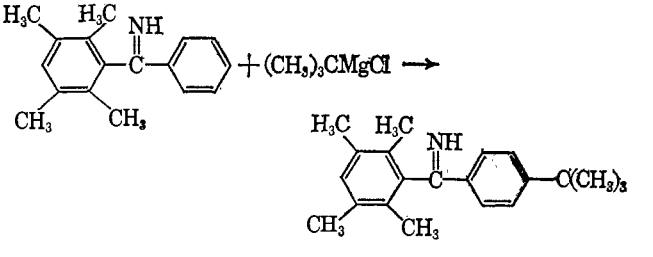
Aliphatic aldimines and ketimines which contain α-hydrogens do not usually react with Grignard reagents in the expected additive manner. These imines react in the enaminic form to reduce the Grignard. N-Isopropylideneaniline reacts with methylmagnesium iodide in amyl ether to give one mole of methane per mole of anil (245). The anil can be quantitatively recovered by hydrolysis of the reaction product.

$$(CH_3)_2C{=}NC_6H_5 + CH_3MgI \rightarrow \left\{\begin{array}{c} CH_4 + CH_2{=}C(CH_3)N(MgI)C_6H_5 \\ \text{III} \\ \text{or} \\ CH_3(CH_2MgI)C{=}NC_6H_5 \\ \text{IV} \end{array}\right\} \xrightarrow{H_2O} (CH_3)_2C{=}NC_6H_5$$

However, Garry (93) has noted that diacetylidene and aniline when refluxed with methylmagnesium iodide in benzene gave 2,3-dimethyl-2,3-dianilinobutane, the normally expected addition product.

Grignard reagents add to imines which contain no α-hydrogens in the usual way (168). N-Benzylideneamines (1 mole) are slowly treated with 2 moles of a Grignard reagent which on hydrolysis gives the addition product in 60 to 90% yields (37). Dessy (63) has found that 2 moles of the Grignard to 1 mole of the imine gives nearly quantitative yields while a 1 to 1 ratio gives somewhat less than 50% yields. These facts are explained if the Grignard reagent is regarded as $R_2Mg \cdot MgX_2$.

Steric inhibition of the addition of Grignards to certain imines has been reported (78). N-Benzylidene-*t*-butylamine does not react with methylmagnesium iodide, while allylmagnesium bromide adds in the usual manner. N-Benzylidenemethylamine, however, reacts with *t*-butylmagnesium chloride. Apparently steric effects are also responsible for the anomalous reaction of *t*-butylmagnesium chloride with duryl phenyl ketimine to give duryl *p*-(*t*-butyl)phenyl ketimine (92).



Reactions other than additions can occur when N-benzylideneamines are treated with Grignard reagents

if certain metal halides are present. For example, N-benzylidenebutylamine and isopropylmagnesium bromide with 2.5 mole % of manganous chloride present give a 55% yield of the bimolecular reduction product 1,2-diphenyl-1,2-dianilinoethane, 17% of the addition product, and 5% of the reduced product benzylbutylamine. Cobaltous chloride in the same reaction gives the reduced product, benzylbutylamine in 98% yield (242). In the manganous chloride (241) reaction, it was found that the yield of bimolecular reduction product increased in the order: isopropylmagnesium iodide < bromide < chloride.

Diaryl ketimines also add Grignards. Diphenylmethylideneaniline and benzylmagnesium bromide gives diphenylbenzylanilinomethane. The *o*-methoxy group of *o*-methoxyphenylphenylmethylideneaniline is readily replaced by a phenyl group in its reaction with phenylmagnesium bromide (91).

Imines, therefore, are analogous to carbonyl compounds in their reactions with Grignard reagents. Enolization, addition, reduction, as well as bimolecular reduction reactions, are possible.

Organolithium compounds apparently react in the same way as do Grignard reagents with imines. Very little has been published mentioning the addition of organolithium compounds to imines. Hurwitz (126) has reported the addition of methyllithium to N-benzylidene-*t*-butylamine, whereas methylmagnesium iodide fails to react with this imine. N-2-Octylideneaniline and methyllithium gives copious amounts of methane and consequently appears to react in the same manner as methylmagnesium iodide (160).

F. ADDITION OF MISCELLANEOUS COMPOUNDS

Many compounds not covered in the above categories also add to imines.

Dialkyl phosphites and thiophosphites add to N-benzylidenenaniline at room temperature under the catalytic effect of sodium ethoxide to give α-anilinobenzylphosphonic acid dialkyl ethers (222, 223).

$$(RO_2)POH + C_6H_5N{=}CHC_6H_5 \rightarrow (RO)_2P(O)CH(C_6H_5)NHC_6H_5$$

These materials also add to aliphatic imines (83, 140).

Hypophosphorous acid adds to N-benzylideneamines in refluxing ethanol to give the aminophosphonic acids. When the amines are aliphatic, 80–90% yields are obtained, when aromatic amines are used the yields are only 30–50% (164, 238).

$$RN{=}CHR' + H_3PO_2 \rightarrow RNHCHR'PO_2H_2$$

Mercaptans add to N-benzylideneanilines at room temperature in benzene solution. Substituents do not affect the addition of the mercaptan to the imine (256, 257).

$$C_6H_5CH{=}NC_6H_5 + RSH \rightarrow C_6H_5CH(SR)NHC_6H_5$$

Gilman (95) reports that mercaptans reduce imines, but Stacy shows this to be due to Gilman's more vigorous reaction conditions of refluxing xylene and a threefold excess of the mercaptan.

When the mercaptan is mercaptoacetic acid, reaction with N-benzylideneaniline gives the cyclic adduct a diphenylthiazolidone (265).

$$C_6H_5CH{=}NC_6H_5 + HSCH_2CO_2H \rightarrow O{=}C(H_2C)(CH(C_6H_5))S{-}N{-}C_6H_5$$

No stable mercaptan addition products of aliphatic aldimines or ketimines have been reported, nor have they been reduced by the use of mercaptans.

N-Benzylideneaniline reacts with ketenes to give lactams at 180–200°. Certain ketenes, such as dicarbethoxyketene, do not react but most do (258).

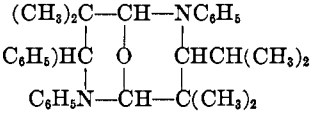
$$C_6H_5CH{=}NC_6H_5 + CH_2{=}C{=}O \rightarrow C_6H_5{-}N(CH(C_6H_5))C(=O)CH_2$$

N-Benzylideneanilines in acetic acid react with potassium isocyanate at 0° in one day to give 1,4-diphenyluretidone (102).

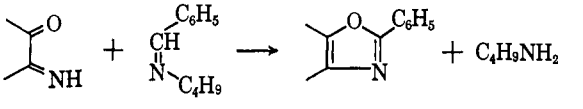
$$C_6H_5CH{=}NC_6H_5 + CH_3CO_2H + KNCO \rightarrow (C_6H_5)HC(NC_6H_5)C(=O)NH$$

Tertiary amyl hypochlorite reacts with anils in carbon tetrachloride on standing at room temperature for 12 hr. to give N,N-diphenylbenzamidine (89, 90).

N-Benzylideneaniline and isobutyraldehyde on standing 1 or 2 days in ethanol gives 2,2-dimethyl-3-phenyl-3-anilinopropylideneaniline, while the mother liquor contains (175)



Retenequinonimine reacts with N-benzylidenebutylamine on elimination of butylamine to give 2-phenylretenoxazole (260).



Benzoyl cyanide and N-benzylideneaniline in ether give N-α-cyanobenzylbenzanilide in 47% yield. The anils from other aromatic ketones as benzophenone (97%), propiophenone (26%), and fluorenone (22%) also react in the same way (67).

$$C_6H_5COCN + C_6H_5CH{=}NC_6H_5 \rightarrow C_6H_5CH(CN)N(COC_6H_5)C_6H_5$$

N-Benzylidenebutylamine in 10% solution of HCN in ethanol when treated with benzoyl nitrile gives β-(butyl-N-benzoylamino)-phenylacetonitrile.

Diphenyl ketimine reacts with nitromethane to give 1,1-diphenyl-2-nitroethylene (68).

$$(C_6H_5)_2C{=}NH + CH_3NO_2 \rightarrow (C_6H_5)_2C{=}CHNO_2 + NH_3$$

Benzoyl chloride and N-benzylideneaniline gives N-α-chlorobenzyl-N-phenylbenzamide (129).

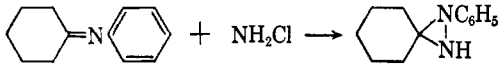
$$C_6H_5CH{=}NC_6H_5 + C_6H_5COCl \rightarrow C_6H_5CH(Cl)N(COC_6H_5)C_6H_5$$

Breederveld (30) has found that acid chlorides add to N-propylidenepropylamine at 10° in benzene solution to form the corresponding N-(1-chloropropyl)-N-propylamides. These materials were not isolated but on heating in the presence of triethylamine were found to dehydrohalogenate to give N-(1-propenyl)-N-propylamides. Acetyl chloride, benzoyl chloride, diethylaminotrichlorosilane, and phosphorous oxychloride all react in this way; silicon tetrachloride and sulfuryl chloride also react but in a different manner which is to be reported later.

$$RCH_2CH{=}NR' + R''COX \rightarrow RCH_2CH(X)NR'(COR'') \rightarrow RCH{=}CHNR'(COR'')$$

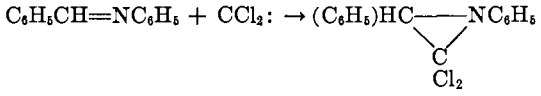
Similarly acetic anhydride added to N-alkylaldimines and eliminated acetic acid to give N-alkyl-N-(1-alkenyl)-acetamides (29).

Chloramines add to imines in ether solution to give diaziridines (239).

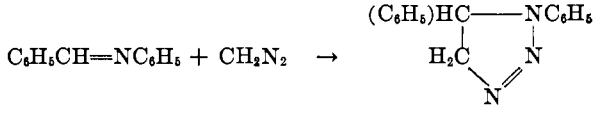


Sodium bisulfite has long been known to add to imines (74), as has hydrogen cyanide (271).

Carbenes have been found to add to N-benzylideneanilines to give ethyleneimines. Dichlorocarbene, from chloroform and sodium methoxide, reacts with N-benzylideneaniline to give the diphenylethylenimine (84). The same carbene but obtained from sodium methoxide and hexachloroacetone undergoes the same reaction (135).



Mustafa (192) was the first to notice that diazomethane reacts with imines to give addition products to which he assigned a 1,2,4-triazoline structure. This addition product was later found to really be a 1,2,3-triazoline (33). Kadaba and Edwards (136) have studied the kinetics of the reaction and found them to



be second order. They also have found that electron-withdrawing groups in the anilino ring increased the reaction rate, while electron-attracting groups decreased the rate. It has also been found that the reaction rate is effected by the solvent in the following order: water > methanol > dioxane > ether. These results strongly indicate that the diazomethane reacts nucleophilically with imines.

Methyl iodide has been long known to add to N-benzylideneaniline to form salts which when hydrolyzed give N-methylaniline and the original aldehyde (56, 142). Methyl sulfate reacts similarly. More recently this reaction has been found to work for aralkyl ketone–aliphatic amine imines (100).

Hantzsch (108) was the first to find that halogens add to imines (Schiff base type). A number of workers subsequently have investigated this reaction. Franzen finds that N-benzylideneaniline when treated dropwise with bromine at room temperature in a carbon tetrachloride, chloroform, or carbon disulfide solution gives the dibromide (87, 88).

$$C_6H_5CH{=}NC_6H_5 + Br_2 \rightarrow C_6H_5CH(Br)N(Br)C_6H_5$$

The dibromide at higher temperatures rearrange to α-bromobenzyl-*p*-bromoaniline. If the bromine addition reaction is carried at higher temperatures, the tribromide is obtained essentially by the bromination of the rearranged dibromide.

$$C_6H_5CH{=}NC_6H_5 + Br_2 \rightarrow C_6H_5CH(Br)N(Br)C_6H_4Br\text{-}p + HBr$$

James (129) also has reported the addition of chlorine and iodine to Schiff bases in carbon tetrachloride. None of the products were characterized except by elemental analysis. Iodine normally gives a tetraiodide which liberates iodine to give a diiodide when exposed to sunlight.

N-Alkylideneamines when treated with bromide in carbon disulfide, benzene, or ether give what is believed to be the α,β-dibromoalkylamine. This is based on the fact that this nonisolable addition product on hydrolysis gives the α-bromoaldehyde and the amine hydrobromide (20, 275).

t-Amyl hypochlorite in carbon tetrachloride gives N-α-amoxybenzyl-N-chlorophenylamine in its reaction with N-benzylideneaniline. The chlorine atom can migrate to the *para* position of the aromatic nucleus if it is unsubstituted. The reverse addition of the chlorine to the carbon rarely occurs (89, 191).

$$C_6H_5CH{=}NC_6H_5 + C_6H_{11}OCl \rightarrow C_6H_5CH(OC_5H_{11})NClC_6H_5$$

Diphenylmethylidene-*o*-toluidine apparently adds sodium or lithium to give either the sodium or lithium salt which when treated with methyl iodide gives the dimethylated compound (180).

$$o\text{-}CH_3C_6H_4N{=}C(C_6H_5)_2 \xrightarrow{Na} o\text{-}CH_3C_6H_4N(Na)C(Na)(C_6H_5)_2 \xrightarrow{CH_3I} o\text{-}CH_3C_6H_4N(CH_3)C(CH_3)(C_6H_5)_2$$

Ingold (127) has found that nitrosobenzene reacts

with N-methylideneanilines to give the four-membered ring 1,2,4-oxadiime.

$$ArN{=}CH_2 + C_6H_5NO \rightarrow \begin{matrix} ArN{-}CH_2 \\ | \quad | \\ O{-}NC_6H_5 \end{matrix}$$

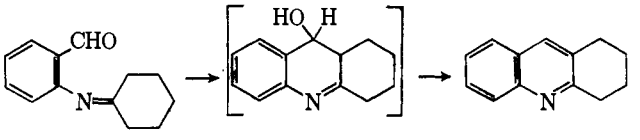
V. Imine–Enamine Isomerization

A. Chemical Evidence

Carbonyl compounds containing α-hydrogens are capable of keto–enol tautomerism. Imines with α-hydrogens would also be expected to be capable of the same type of isomerization.

$$RN{=}C(R')CHR''R''' \rightleftarrows RNHC(R'){=}CR''R'''$$

Such an isomerization has been clearly demonstrated in many cases by reactions involving α-hydrogens of imines. For example, N-cyclohexylidene-2-aminobenzaldehyde undergoes cyclization to 1,2,3,4-tetrahydroazaanthracene (26).



Methylmagnesium iodide reacts with N-isopropylideneaniline (242) to give methane and the α-hydrogen organometallic intermediate $CH_3(CH_2MgI)C{=}NC_6H_5$. Marekov and Petsev (173) have recently demonstrated that when N-1-phenylethylideneaniline reacts with isopropylmagnesium chloride propane is liberated and the organometallic product when treated with benzaldehyde or diphenyl ketone gives the α,β-unsaturated imine. They feel that the organometallic product has the structure

$$C_6H_5N{=}C(C_6H_5)CH_2MgCl + C_6H_5CHO \rightarrow C_6H_5N{=}C(C_6H_5)CH{=}CHC_6H_5 + H_2O$$

This represents a reaction of the α-hydrogen of the imine.

Turcan (275, 277) in the bromination of N-pentylidenepentylamine obtains (1,2-dibromopentyl)pentylamine (not isolated) which when hydrolyzed gives α-bromovaleraldehyde and the amine. He interprets these results to indicate that the bromine adds to the carbon–carbon double bond of the enamine tautomer rather than the carbon–nitrogen bond of the imine.

$$CH_3CH_2CH_2CH{=}CHNHC_6H_{11} + Br_2 \rightarrow CH_3CH_2CH_2CH(Br)CH(Br)NHC_6H_{11}$$

Acylation of the α-carbon of aliphatic ketimines can be accomplished with either ketene or acetic anhydride (113).

Acetic anhydride in acetic acid at 140 to 180° reacts with N-2-(4-methylpentylidene)-1,3-dimethylbutylamine to give 4-(2-oxo-6-methylheptylidene)-1,3-dimethylbutylamine which is not isolated but hydrolyzed to the diketone.

$$RN{=}C(CH_3)R' + (CH_3CO)_2O \rightarrow RN{=}C(CH_2COCH_3)R' + CH_3CO_2H$$

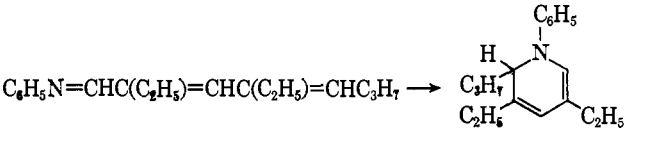
Ketene reacts with N-2-(4-methylpentylidene)aniline at 5 to 10° and hydrolyzes to give isovalerylacetone.

$$C_6H_5N{=}C(CH_3)CH_2CH(CH_3)_2 + CH_2{=}C{=}O \rightarrow C_6H_5N{=}C(CH_2COCH_3)CH_2CH(CH_3)_2 \xrightarrow{H_2O} CH_3COCH_2COCH_2CH(CH_3)_2 + C_6H_5NH_2$$

It will be noted that the methyl group is acylated in preference to the methylene group. Where no methyl group is present a methylene group may be acylated but with more difficulty. N-4-(2,6-Dimethylheptylidene)alkylamines are only monoacetylated with ketene.

Benzoyl chloride has also been reported to benzoylate imines in the α-position (198).

In the preparation of aliphatic aldimines and ketimines reference is made to aldol condensation side reactions. These can also be used to serve as evidence for the existence of imine–enamine tautomerism. N-Butylidenebenzylamine reacts with butyraldehyde to give a 94% yield of N-2-ethylhexen-2-ylidenebenzylamine (206). Aliphatic aldimines when heated and then hydrolyzed were found to have undergone aldol condensation reactions to give the α,β-unsaturated aldehydes (273). Aniline when reacted with butyraldehyde in the presence of acetic acid has been shown to give as the main product N-phenyl-3,5-diethyl-2-propyl-1,2-dihydropyridine (50, 233). This reaction probably results from tautomerization and ring closure of the following aldol condensation product.



Another α-hydrogen reaction that imines undergo is cyanoethylation. N-Butylidenecyclohexylamine with a fivefold excess of acrylonitrile at 150° under nitrogen gives a 73% yield of N-2-cyanoethylbutylidenecyclohexylamine (150). The methylene hydrogen reacts in preference to the methyl hydrogen in the case of N-2-pentylidenecyclohexylamine. Generally cyanoethylation stops at the monosubstituted state but in the case of N-cyclohexylidenecyclohexylamine either the mono- or the di- (2,6-positions) cyanoethylated products could be obtained (151).

Phenylisothiocyanate and N-1-phenylethylideneaniline react at 130–140° to give the thioamide of the imine (187).

$$C_6H_5C(CH_3){=}NC_6H_5 + C_6H_5NCS \rightarrow C_6H_5N{=}C(C_6H_5)CH_2C(S)NHC_6H_5$$

Oxidation of N-2-phenylpropylideneanisidine gives N-2-phenyl-2-hydroperoxypropylideneanisidine which

is the oxidation of the carbon–hydrogen bond α to the imino group (283).

$$p\text{-}CH_3OC_6H_4N{=}CHCH(C_6H_5)CH_3 \xrightarrow{O_2} p\text{-}CH_3OC_6H_4N{=}CHC(OOH)(C_6H_5)CH_3$$

B. PHYSICAL EVIDENCE

von Auwers (8) using physical measurements of imines, molar refractions, states that imines ordinarily exist in the imino form in spite of the fact that they may sometimes react in the enamino form as has been indicated above. For example, imines obtained from ketones of the type $RCOCH_2$alkyl or -aryl are true imines; however, if obtained by an indirect route they are as stable as the enamine. Imines derived from ketones of the type $RCOCH_2COR$, $RCOCH_2CO_2R$, or $RCOCH_2CN$ exist as enamines although under certain conditions they can exist as imines. His conclusions to date have been verified by other workers using other physical measuring methods.

Infrared and Raman spectra of N-alkylidenemethylamines show that they exist as imines with no tautomerization to the enamine being detected (137). In contrast to these results, N-cyclohexylidenecyclohexylamine shows the presence of both imine and enamine isomers (21). Witkop (283), however, found no evidence for the presence of the enamine in his infrared studies. Ethyl β-aminocrotonate, 2-carbethoxycyclopentylidenimine, and 2-carbethoxycyclohexylidenimine exist only as enamines, while 2-phenylpropylidenimine and 2,2-diphenylethylidenimine exist only as imines. More recently nuclear magnetic resonance studies show that the monoimine of acetylacetone exists as the enamine to the extent of 95% or more (71).

In contrast to the above results Dabrowski (55) claims that $PrCOCH{=}CHNH_2$ can be separated from $PrC(OH){=}CHCH{=}NH$ by a continuous extraction at $-25°$ with ether. Optically active α-phenylethylamine was condensed with aceto-acetic ester at $-10°$ in ether and two isomers were isolated. Mutarotation of the two isomers showed that the enamine to imine ratio was 68 to 32 at equilibrium (219).

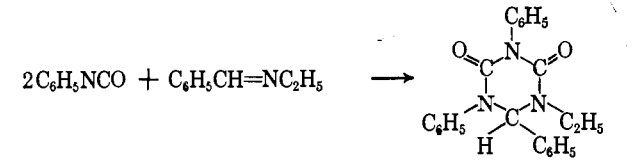
It seems that imine–enamine tautomerism is similar to keto–enol tautomerism and with the rather recent common usage of nuclear magnetic resonance, this field of tautomerization could shortly be more clearly defined.

VI. MISCELLANEOUS REACTIONS OF IMINES

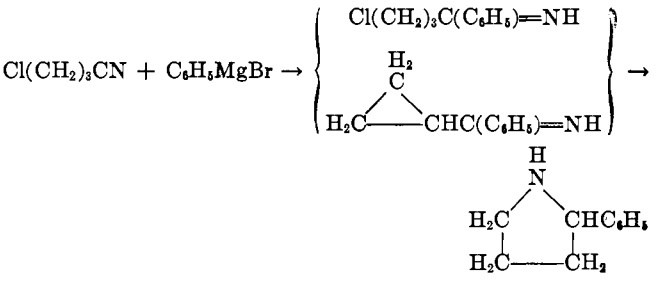
A. REACTIONS INVOLVING RING FORMATION

N-Benzylideneaniline when heated to 800° was found to give phenanthridine in a 2% yield. Earlier Pictet (216) had found that N-benzylidene-*o*-toluidene when passed through a hot tube gives 2-phenylindole in a 30% yield (215).

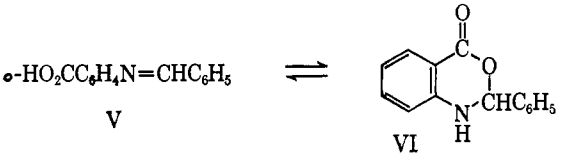
When N-benzylidenepropylamine is treated with 2 moles of hydrocyanic acid 1-propyl-6-phenyl-2,4-diketohexahydrocyanidene is obtained (103), while phenyl isocyanate and N-benzylideneethylamine (156) at 200° react as shown.



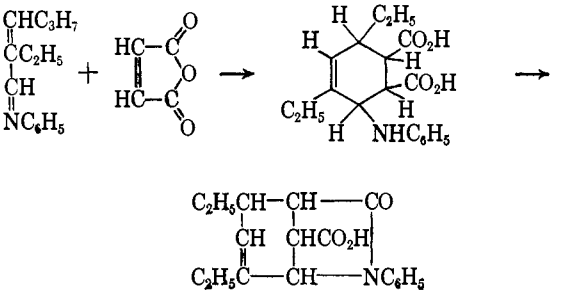
2-Phenylpyrrolidine is formed from cyclopropyl phenyl ketimine or ω-chloropropyl phenyl ketimine, which is the reaction intermediate formed from phenylmagnesium bromide and ω-chloropropylnitrile (43, 44).



N-Benzylidene-*o*-aminobenzoic acid exists as an equilibrium mixture of open and cyclized isomers and in reactions with acetic anhydride and phenyl isocyanate gives the N-acylated derivatives of the cyclic isomer VI (249).

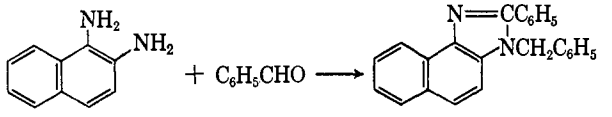


Snyder (247, 250) has also found that N-2-ethylhexen-2-ylideneaniline and maleic anhydride in refluxing benzene gives a Diels–Alder type reaction product in 80% yield. This material then cyclizes to the amide: 5,7-diethyl-2-phenyl-2-azatricyclo-[2.3.1]-oct-6-ene-3-onecarboxylic acid.



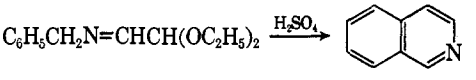
Cinnamylideneaniline does not react since it has no ϵ-hydrogen atom which must tautomerize if the reaction is to work. The reaction essentially involves the enamine rather than the imine.

1,2-Diaminonaphthalene reacts with excess benzaldehyde to give only the monoimine 2-N-benzylidene-1,2-diaminonaphthalene. However, in the presence of hydrogen chloride, N-benzyl-C-phenylnaphth[1,2]imidazole is formed (167).

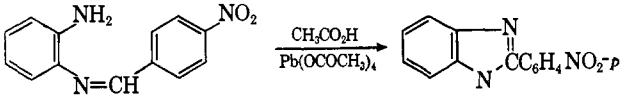


Diazomethane in methanol reacts with N-1-hydroxy-2-naphthylidene-α-naphthylamine to give 3-(α-naphthylamino)-4:5-benzocumaran, but no reaction occurs in ether (243).

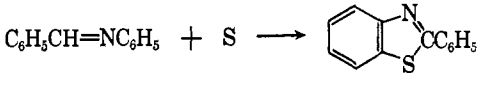
An improved Pomeranz–Fritsch isoquinoline synthesis utilizes N-2,2-ethoxyethylidenebenzylamine which is cyclized with sulfuric acid. Polyphosphoric acid and phosphoryl chloride are also effective catalysts, and the thienylideneamine can also be cyclized (118, 237).



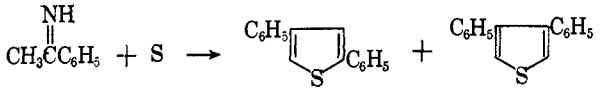
N-Nitrobenzylidene-*o*-phenylenediamines are oxidized with lead tetraacetate in acetic acid to give the nitro-substituted benzoxazoles (262, 263).



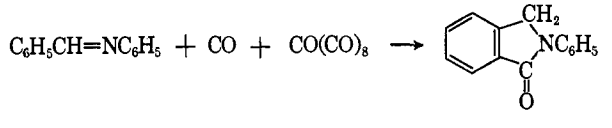
N-Benzylideneaniline and sulfur at 280° gives 2-phenylbenzathiazole (27).



N-Phenylethylideneaniline when heated with sulfur at 220–240° gives mostly 2,4-diphenylthiophene with some 2,5 isomer (61). Selenium gives only the 2,4 isomer.

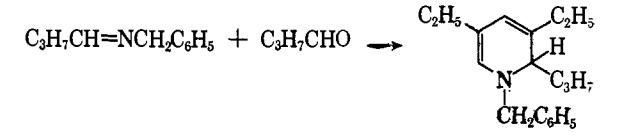


N-Benzylideneaniline, benzene, carbon monoxide, and cobalt octacarbonyl at 200 atm. give 2-phenylphthalmidine in 80% in 56 hr. High temperatures in a silver-lined vessel shortens the reaction time to 1 hr. (190, 221).

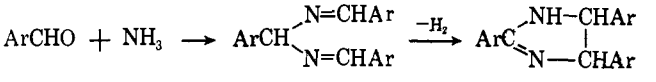


Anils of aralkyl ketones can be cyclized at 500–575° using a $CuCr_2O_4$, Cr on Al_2O_3, or active carbon catalyst. For example, 1-phenylethylideneaniline gives 2-phenylindole. Similarly 1-phenylpropylideneaniline gives 2-phenylquinoline. The imine is converted to the heterocyclic in from 5 to 30% yield per pass (106).

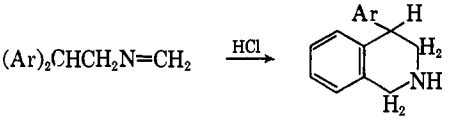
N-*n*-Butylidenebenzylamine when refluxed with butyraldehyde gives the aldol condensation product, N-2-ethylhexen-2-ylidenebenzylamine, in 42% yield and a cyclic material in 32% (206).



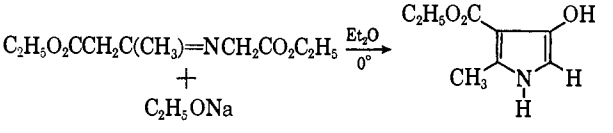
Aromatic aldehyde reacts with ammonia to give a diimines which cyclize to 2,4,5-triaryldihydroimidazoles (75).



N-Methylidene-β,β-diarylethylamine is cyclized with concentrated hydrogen chloride to give 4-aryl-1,2,3,4-tetrahydroisoquinoline (62).

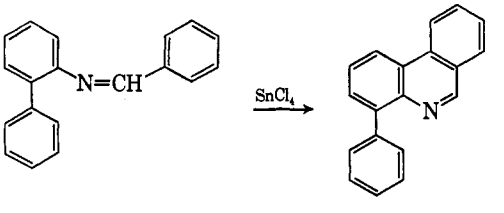


The imines of β-oxoacid ester, β-diketones, and β-oxoaldehydes are cyclized to β-hydroxypyrroles (274).



Anils of acetylacetone when treated with concentrated acids are cyclodehydrated to 2,4-dimethylquinolines (25).

N-Benzylidene-2-phenylaniline is also cyclized in stannic chloride in refluxing *o*-dichlorobenzene, or with phosphorus pentachloride in trichlorobenzene. Aluminum chloride or phosphorus oxychloride are less effective in catalyzing this reaction (16).



B. REACTIONS OTHER THAN CYCLIZATIONS

N-Benzylideneethylamine is thermally cracked when passed over a nickel catalyst at 420° to give toluene, ethylamine, phenyl cyanide, and ethane.

Nitrosyl chloride or sulfate react with N-benzylideneaniline at 0° in benzene to give the diazonium salt and benzaldehyde.

$$C_6H_5CH{=}NC_6H_5 + NOCl \rightarrow C_6H_5N_2{}^+Cl^- + C_6H_5CHO$$

Aliphatic imines are not described (277).

Carboxylic acids react with N-benzylideneaniline to give the N-acylated aniline. Acid anhydrides give the acylated anilines (94, 165).

Aliphatic ketimines when passed over quartz at 375° give nitriles (3). Unsaturated imines and ammonia give nitriles when passed over a copper–zinc or silver–zinc catalyst at 300–400° (270).

$$(CH_3)_2CHCH{=}NCH{=}C(CH_3)_2 + NH_3 \rightarrow (CH_3)_2CHCN \quad 93\%$$

N-Benzylidenemethylamine and formamide react 105–130° in 4 hr. to give N-benzylformamide (46%) and the dibenzylformamide (24%) (244).

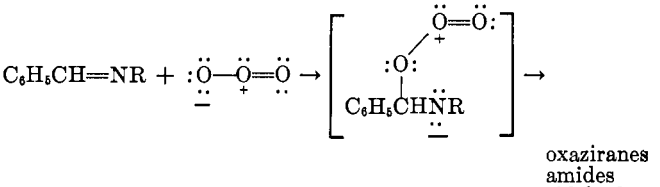
$$HCONH_2 + C_6H_5CH{=}NCH_3 \rightarrow C_6H_5CH_2NHCHO + (C_6H_5CH_2)NCHO$$

The same imine gives N-methylthiobenzamide when heated with sulfur at 200°. Schiff bases also give thiobenzamides but cyclization to the 2-arylbenzathiazoles also occurs (27).

$$C_6H_5CH{=}NCH_3 + S \rightarrow C_6H_5C(S)NHCH_3$$

N-Methylbenzamide is obtained in a 60% yield on treatment of N-benzylideneaniline with N-chloromethylamine and sodium hydroxide (239).

Bailey (225) recently has studied the ozonization of imines. He has ozonized N-benzylidene-*t*-butylamine in ethyl acetate followed by a treatment with a sodium hydroxide solution to give N-*t*-butylbenzamide (24%), 2-*t*-butyl-3-phenyloxazirane (15%), and benzoic acid (40%). N-Cyclohexylideneisobutylamine and ozone give cleavage products with cyclohexanone being isolated in a 50% yield. Similarly N-benzylideneaniline gives benzaldehyde in high yields. In both of these instances the oxaziranes are known to be unstable. These results are explained on the basis of ozone acting as a nucleophilic reagent rather than as an electrophilic one as is customarily found.



oxaziranes
amides
aldehydes

Miller (181) in the ozonization of N-benzylidene-*p*-chloro- or *p*-nitroaniline obtains the cleavage products—benzaldehyde (40%) and *p*-chloro- or *p*-nitronitrobenzene (10–14%). N-Cinnamylideneaniline reacts with ozone predominantly at the carbon–carbon double bond since benzaldehyde was obtained in 60% yield. Formanilide was also obtained again indicating a nucleophilic reaction at the imino carbon.

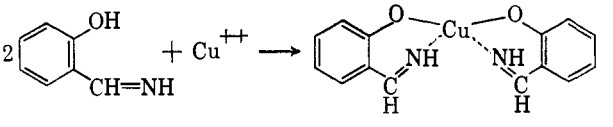
Peracetic acid treatment of aliphatic ketimines gives nitrosoalkanes in 30 to 90% yields and the ketones. An unstable oxazirane intermediate is postulated (79).

$$(C_2H_5)_2C{=}NCH_2C_6H_5 + CH_3CO_2H \rightarrow (C_2H_5)C{=}O + C_6H_5CH_2NO$$

The methiodide of diphenyl ketimine has a strong positive charge on the imino carbon and can react with nucleophilic reagents to give the C-substituted compounds. Potassium cyanide, Grignard reagents, water, and ammonia have been treated with this compound to give the expected reaction products (117).

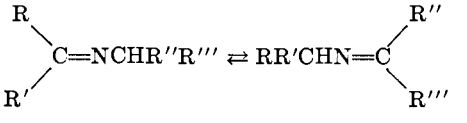
$$(C_6H_5)_2C{=}N(CH_3)_2{}^+I^- + KCN \rightarrow (C_6H_5)_2C(CN)N(CH_3)_2 + KI$$

Certain imines can form complexes with metals. Imines which form such complexes are about the same as those carbonyl compounds which form similar complexes. They have the general characteristics of forming a five- or a six-membered ring with the metal. The ring also contains one or two double bonds. For example, imines of salicylaldehyde complex with metals (208).

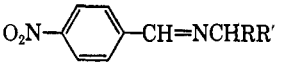


VII. Triad Protropy of Imines

Imines exhibit a type of tautomerism of which carbonyl compounds are incapable. Since imines can be substituted on both the carbon and nitrogen of the imino group with hydrogen containing groups, the following type of tautomerism is possible.



This tautomerism is base-catalyzed and is generally carried out by refluxing the imine in ethanol containing sodium ethoxide. Not in the case of every imine will this tautomerism be observed. Baddar shows that for compounds of the type



where R is methyl and R′ is hydrogen or constitutes a ring structure no tautomerism is noted in boiling pyridine (10). However, if R or R′ is a carboxyl group, tautomerism is observed. Later he shows that in the equilibrium

$$RCH_2N{=}CHR' \rightleftarrows RCH{=}NCH_2R'$$
VII VIII

VII is favored by an increase in the electron attraction of the R group (11). It has been shown that the rate of loss of optical activity of the system

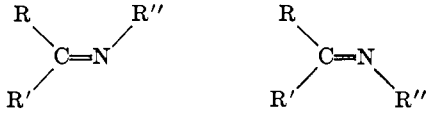
$$C_6H_4(R)CHN{=}CHC_6H_5 \rightleftarrows C_6H_4(R)C{=}NCH_2C_6H_5$$

in an ethanol–dioxane solution at 50° and catalyzed by sodium ethoxide decreases in the order, where R is, H > Me > Et > *i*-Pr > *t*-Bu. This is accounted for on the basis of the increased inductive effect in the same order (199). That substituents are determinant in the equilibrium mixture obtained from such a tautomerism can be seen in the equilibria obtained with various pyridoxylidenebenzylamines (284).

This type of tautomerism is considered to be rather immobile and strong nucleophilic catalysts are necessary for tautomerism to occur (128).

VIII. *syn–anti* Isomerization of Imines

The fact that imines possess a double bond suggests that geometric isomers should be possible.

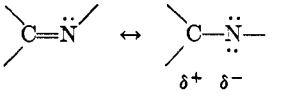


Early workers did report the isolation of *syn* and *anti* isomers. N-Salicylidene-*p*-carbomethoxyaniline was found to exist as yellow needles which melt at 145°. These needles when exposed to light are converted to orange-red needles which melt at 259° (171). This was attributed to the isolation of the *syn* and *anti* isomers of this compound. Anselmino (5) felt that these were not necessarily geometric isomers but perhaps were the result of polymorphism. This view was indicated to be correct when dipole moment studies of substituted benzylideneanilines indicated that they existed only in the *anti* form (57). The dipole moments of N-salicylidene-*p*-carbethoxyaniline, both the red and yellow forms, have been found to be the same, consequently only one geometric isomer exists, although in two forms (58, 133).

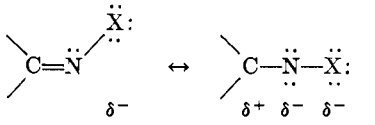
Aliphatic and aromatic imines, including N-salicylidene-*p*-carbethoxyaniline, were investigated in the ultraviolet and visible regions before and after illumination with ultraviolet light for 5 to 6 hr. All of the imines investigated showed no difference in the absorption spectra. Consequently, no isomerization was noted, and it was concluded that all the materials tested exist in the *anti* form (119).

Taylor and Fletcher (267) feel that they have observed geometric isomerization in the case of N-2-nitrofluorenylidene-*p*-toluidine. The two isomers they isolated on treating 2-nitrofluorenone with *p*-toluidine in the presence of an acid have differences in both the ultraviolet and infrared spectra. Curtin and Hausser, however, feel that these results should be held as tentative until further work is done, since they find one of the "isomers" on recrystallization several times gives a material of higher melting point and whose composition is not correct for the imine. Curtin and Hausser (53) are the first workers to demonstrate that imines are capable of existence in *syn* and *anti* isomer forms, that is, if Taylor and Fletcher's work is subsequently proven incorrect. They have measured the rate of isomerization of the imine obtained from *p*-nitro- or *p*-chlorobenzophenone dichloride and methylamine. Crystalline *p*-chlorobenzophenone methylimine exists as the *syn* isomer (the *p*-chlorophenyl and the methyl groups on the same side of the double bond). The *p*-nitro compound exists as the *anti* isomer. In cyclohexane, at room temperature or above, these pure materials isomerize to an equilibrium mixture of the *syn* and *anti* isomers. The rate of isomerization is very rapid but could be followed and determined by ultraviolet spectroscopy. The corresponding imines obtained from arylamines on crystallization give only one isomer which isomerizes too rapidly in solution to an equilibrium mixture to be followed instrumentally. The solution of these materials again shows an equilibrium of *syn* and *anti* isomers as determined by nuclear magnetic resonance spectroscopy. This work then represents the only case where geometric isomerism of imines appears to be definitely demonstrated. Even in this case, however, isolation of separate *syn* and *anti* isomers has not been accomplished. Mutarotations of substituted N-benzylidenebenzylamines in the pure state and in solution have recently been used to suggest *syn–anti* isomerization of these imines. More work in this area is in process to further substantiate these findings.

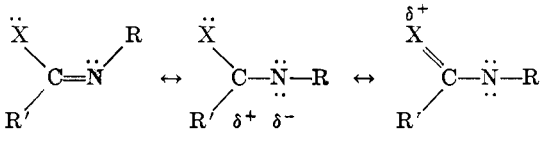
The fact that imines cannot be isolated in both *syn* and *anti* forms must be due to the ease of free rotation about the carbon–nitrogen double bond. This probably arises from the fact that the electronegativity of the nitrogen compared to that of the carbon causes a lowering of the double bond character of the imino linkage by a polarization.



No such polarization forces are at work in the case of stilbene nor azobenzene where the geometric isomers have been isolated. Azoxybenzene also gives stable isomers. A number of materials which contain an imino group do have isolable *syn* and *anti* isomers. For example, oximes, semicarbazones, and N-chloro- or bromoimines exist in two stable forms (268). From this data it might be suggested that the presence of electronegative groups on the nitrogen of the imino group decrease the polarization that normally occurs by an electrostatic repulsion due to adjacent negative changes in the following resonance structures.



This would give the imino group more double bond character and would allow geometric isomers to be separable. In contrast to this, imide chlorides and imidates which have an electronegative group on the imino carbon exist only in the more stable *anti* configuration (46, 99). These groups could facilitate the polarization of the imines group by their resonance contributions



Here again a very interesting area of chemistry remains to be resolved.

The author wishes to acknowledge Drs. W. Semon, D. Craig, R. Strassburg, and R. Fawcett for their critical reading of this review and their helpful suggestions.

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