THE CHEMISTRY OF THE ALKALI AMIDES. III

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This review of the chemistry of the alkali amides is a continuation of two earlier reviews (17) which have appeared on this subject. In the present review the authors have summarized the work on the inorganic and organic chemistry of the alkali amides which has appeared in the literature from 1937 through 1952. In addition, a considerable amount of previously unpublished material is discussed. Whenever possible, the authors have tried to interpret and evaluate critically the material presented and to call attention to those areas of research which have not been investigated or which should be studied further. Although it has not been convenient to discuss all of the present material under the same headings as were used previously, the changes have not been so extensive as to make cross references difficult.

PART I. PREPARATION, PROPERTIES, AND INORGANIC REACTIONS OF THE ALKALI AMIDES

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CONTENTS

I. INTRODUCTION

Very little of importance has been added to our knowledge of the physical properties and inorganic reactions of the alkali amides during the period 1937–52. In fact, the paucity of publication in these areas stands in sharp contrast to the voluminous publication in the area of organic chemistry. The interpretation of reaction mechanisms among organic compounds and the further developments of synthetic methods based on the alkali amides would be definitely aided by information which can be obtained from physical-chemical studies. Among the

items needing study for this or other reasons are: the solubility of lithium, calcium, and barium amides in liquid ammonia; the solubility of all of the alkali and alkaline earth amides in a wide variety of organic solvents (non-protonic); accurate values for the relative base strength of the various metal amides; phase studies of mixtures of two amides (50), of mixtures of a metal amide and a metal hydroxide, of mixtures of a metal amide and a metal hydride, and of mixtures of a metal amide and a simple salt; and the photoconductance of solutions of the metal amides in liquid ammonia. Similarly, in the area of reactions of the alkali amides with inorganic compounds, much more remains to be done than the total of what has been accomplished so far. In particular it would be interesting to establish the relationship between the recently prepared double nitrides (LiMgN, LiZnN, Li_3AlN_2, Li_3GaN_2) (42, 43, 44) and the familiar double amides (ammonometallates).

II. HISTORICAL

Perhaps the most significant event concerning the alkali amides during the period covered by this review is their widespread acceptance as laboratory reagents. This is due in large part to the development of a convenient laboratory synthesis (92) and in smaller part to the commercial availability of lithium and sodium amides. Although sodium amide had been used industrially for many years prior to 1946, it had not been available on the market until that time. The reason usually given for this situation was the fear created by several bad accidents (undoubtedly caused by oxidation products) in handling sodium amide. If the amides are consumed as they are made, there is no danger in their use. Likewise, if the amides *are handled and stored properly*, they present no hazard.

III. THE ALKALI AMIDES AS THE CAUSTIC ALKALIS OF THE AMMONIA SYSTEM

A. Action on indicators; neutralization reactions

Most of the statements in the literature as to the behavior of indicators in liquid ammonia would lead the reader to feel that the phenomenon is strictly comparable to that in water solution. However, there are distinct differences of behavior in the two solvents. Although ammonia, like water, is amphiprotic,

$$2NH_3 \rightleftharpoons NH_4^+ + NH_2^-$$

the affinity of the ammonia for the proton is so much greater than that of water for the proton that ammonia is predominantly a basic solvent. Consequently, indicators which are weak acids are completely dissociated in ammonia and indicators which are weak bases are completely undissociated. Thus, in most cases, when an indicator is dissolved in liquid ammonia, it exhibits the same color that it would in a basic aqueous solution; the addition of ammonium ion does not alter this color nor does the addition of a solution of an amide unless there is some specific interaction with the indicator molecule (82, 83). This specific interaction may be reversible if the indicator functions as a very weak acid toward

the strong base, or irreversible if the amide reacts to alter the composition of the indicator (halogen-containing indicators, certain nitro compounds, etc.).

The mono- and polynitrophenols are colorless in acid solution and yellow or orange yellow in basic solution. These substances are yellow or orange in pure liquid ammonia or in solutions of ammonium salts in liquid ammonia; in dilute solutions of potassium amides, the mononitrophenols exhibit no change in color, whereas the polynitrophenols give precipitates. In concentrated solutions of potassium amide, *m*- and *p*-nitrophenols exhibit a red color. The nitroanilines behave similarly in pure ammonia and solutions of ammonium salts but give evidence of specific interaction with the amide ion. Several azo indicators exhibit their basic colors in ammonia and solutions of ammonium salts. The same color is shown in dilute alkali amide solutions except for *p*-benzeneazoaniline (red instead of yellow) and *o*-tolueneazo-*o*-toluidine (violet instead of yellow). Concentrated potassium amide solutions give rise to different colors in several instances: *p*-benzeneazodimethylaniline (violet red), methyl orange (red brown), and *p*-tolueneazodimethylaniline (violet).

A number of indicators, especially the phthaleins and sulfonphthaleins, show the same change on cooling from room temperature to −33°C. that they exhibit in dilute solutions of the alkali amides. This change on cooling takes place whether or not ammonium ion is present (10, 80).

It is evident that much yet remains to be done in order to develop a set of indicators which will be suitable for the accurate study of proton availability (ammonium-ion activity) in liquid ammonia solution. However, a number of indicators have been found which appear to give reversible color changes depending upon the presence in the solution of excess ammonium ion or amide ion (10, 80, 81).

The heats of reaction of a solution of potassium amide with solutions of ammonium salts (500 moles of solvent per mole of salt) have been measured (58) with the following results: ammonium iodide, 26.1 kcal.; ammonium nitrate, 26.1; ammonium thiocyanate, 26.7; ammonium bromide, 25.1.

The dipotassium salt of sulfamic acid can be prepared by the interaction of excess potassium amide with ammonium sulfamate in liquid ammonia. The product is obtained first as a gelatinous precipitate which becomes finer and presumably microcrystalline on standing (14). Molybdenum(VI) oxide 3-ammoniate, presumably the diammonium salt of a mixed aquoammonomolybdic acid, forms a yellow tripotassium salt with potassium amide in liquid ammonia at room temperature (97):

$$(NH_4)_2HMoO_3N + 3KNH_2 \rightarrow K_3MoO_3N + 5NH_3$$

The reaction goes to completion only very slowly even in the presence of a large excess of potassium amide.

B. Precipitation of insoluble bases

An impure cerium(III) amide is obtained by the reaction of potassium amide on cerium(III) thiocyanate in liquid ammonia solution (12).

Titanium(III) amide, $Ti(NH_2)_3$, is obtained as an insoluble, green-black, amorphous precipitate (somewhat contaminated with potassium ammonotitanate) by the reaction of potassium amide with $K_3Ti(SCN)_6$ in liquid ammonia (79). Titanium(III) amide does not form an ionic lattice but is a highly polymeric substance. A white, insoluble, impure zirconium(IV) imide is obtained by the reaction of a solution of potassium or potassium amide on the product of ammonolysis of zirconium(IV) bromide, $3Zr(NH)_2 \cdot 7NH_4Br \cdot xNH_3$ (21).

The mixing of solutions of potassium amide and $K_3V(SCN)_6$ results in the precipitation of dark black, finely divided vanadium(III) amide, $V(NH_2)_3$, containing considerable potassium and some thiocyanate as impurities (74).

Bright red chromium(III) amide, $Cr(NH_2)_3$, precipitates when solutions of hexamminechromium(III) nitrate and potassium amide are mixed. Similarly, brown cobalt(III) amide is precipitated through the interaction of hexamminecobalt(III) nitrate and potassium amide in liquid ammonia (72, 78). The amides of chromium and cobalt are considered to be highly polymeric materials.

C. Amphoteric amides

Moderately soluble potassium ammonoindate is obtained by the action of excess potassium amide on indium(III) bromide followed by recrystallization and washing (88). In the presence of an excess of potassium amide, titanium amide is converted (79) to bright olive-green potassium diimidotitanium(III), $K[Ti(NH)_2]$. The potassium ammonozirconate, $Zr(NK)_2 \cdot 2NH_3$, obtained by the reaction of excess potassium amide on ammonobasic zirconium(IV) bromide, is difficult to obtain in a pure state because of its ready ammonolysis (21).

The action of an excess of potassium amide on $K_3V(SCN)_6$ [or $V(NH_2)_3$] produces black potassium diimidovanadate(III), $K[V(NH)_2]$ (74). The same product has been obtained [contaminated by adsorbed potassium amide or admixed vanadate of higher potassium content, V(NHK)NK] by the action of a solution of potassium amide or potassium upon the ammonolytic product of vanadium(III) bromide (25). A dark yellow mixture of insoluble potassium ammonotantalates, $Ta(NH_2)_4NHK$ and $Ta(NH_2)_3(NHK)_2$, is obtained by the reaction of excess potassium amide on the product of ammonolysis of tantalum(V) bromide (53).

Potassium amide reacts with antimony(III) nitride or ammonobasic bromide to form an insoluble potassium ammonoantimonite, $Sb(NH_2)NK$, contaminated with a similar salt of higher potassium content (91).

Chromium(III) amide and potassium amide react to form an ammonochromate(III) of the composition $K_n[Cr(NH_2)_4]_n$, whereas hexamminechromium(III) iodide and potassium amide form $K_n[Cr(NH_2)_2NH]_n$. Both of these compounds are thought to be polymeric. Cobalt(III) amide and potassium amide form a black nitrido salt of the composition $K_3Co_2N_3$ (72, 78).

D. Ammonobasic salts

When a solution of potassium amide is added to a solution of cerium(III) iodide at 0°C., a basic salt of the composition $Ce_2I_3N_{13}H_{36}$ is precipitated. At

150–180°C. this becomes $Ce_2I_3N_2H_3$. There is some evidence for the existence of a soluble ammonobasic cerium(III) thiocyanate (12).

Soluble ammonobasic salts, probably of the type $[Ti(NH_2)_2(NH_3)_2]_nX_n$, are formed in the reaction of ammonium thiocyanate upon titanium(III) amide (79).

Chromium amide dissolves in a liquid ammonia solution of ammonium bromide to form a deep red compound of the composition $Cr(NH_2)_3 \cdot NH_4Br \cdot HBr$ which is undoubtedly a polynuclear complex of the type $[(NH_3)_3Cr(NH_2)Br]_nBr_n$. Cobalt amide reacts analogously with ammonium salts, and the compound $[(NH_2)_2Co(NH_3)_2]_n(NO_3)_n$ has been isolated from the dark brown solution (72). When chromium amide (76) and cobalt(III) amide (75) are heated with a liquid ammonia solution of ammonium nitrate at temperatures near 100°C. for several days, they are converted quantitatively to hexamminechromium and -cobalt(III) nitrates, respectively.

E. Basic catalysis

Just as a base catalyzes aquation in many instances, a trace of sodium amide catalyzes the conversion of $[Cr(NH_3)_5Cl]^{++}$ to $[Cr(NH_3)_6]^{+++}$ (67).

IV. PREPARATION OF THE ALKALI AMIDES

Detailed directions for the preparation of sodium amide by the reaction of gaseous ammonia with molten sodium have appeared in several places (15, 27). An interesting modification of this procedure as applied to lithium amide (or alkaline earth amides) is that of Alexander (9, 34). Lithium oxide is heated with magnesium (aluminum, silicon, ferrosilicon, etc.) in an atmosphere of ammonia at a temperature of 500–900°C. (preferably 700°C.). The lithium liberated by the magnesium is converted to the hydride by the hydrogen from the dissociation of ammonia. The temperature is lowered to 300–500°C. (400°C. preferred), additional ammonia is admitted to convert the hydride to amide, and the latter is distilled (b.p. 430°C.) to a cooler part of the retort.

The synthesis of sodium amide directly from the elements:

$$Na + 0.5N_2 + H_2 \rightarrow NaNH_2$$

is possible at pressures greater than 30–50 atm. and at reaction temperatures of 350–450°C. Under the most favorable conditions (50 atm., 350°C.) 93 per cent of the metallic sodium is changed to sodium amide (69).

A further modification of the preparation of alkali amides is that of causing an alkali metal and ammonia to react in an inert medium, such as paraffin oil, lubricating oil, dimethylaniline, or decahydronaphthalene, in the presence of known catalysts (63, 64). Since sodium amide when cooled from the molten condition is difficult to pulverize, Truthe has studied the granulation of sodium amide and other materials by causing the melt to impinge on rapidly rotating disks with rapid cooling and quenching by unreactive gases (28).

Shreve *et al.* (85) describe a "ball-mill reactor" for the generation of sodium amide. The reaction between sodium and ammonia is carried out in a ball mill

equipped with special fittings (for introduction of gaseous ammonia and heating), and the molten sodium amide is cooled under pulverizing conditions.

However, it is the method originally proposed by Vaughn, Vogt, and Nieuwland (92), which involves the catalyzed reaction between liquid ammonia and dissolved alkali metals, that has become common practice in most laboratories. The reduction products of ferric chloride and sulfate (57) and of cobalt and nickel salts (61) as well as those of ferric nitrate are catalytically active. This preparation is described in detail in *Inorganic Syntheses* (33) and is the subject of two patents (57, 61). Further, the method has been adapted to the preparation of other amides: lithium amide (35, 61), potassium amide (84), and barium amide (59).

Additional observations on the catalytic effect of various substances for the conversion of dissolved metal to amide have been made. Thallium is a catalyst for the conversion of potassium, rubidium, and cesium to the amides, while gallium is a catalyst for the conversion of sodium (102).

Burgess and Kahler (22) studied this catalytic effect and determined the most appropriate catalysts, both foils and powders. For various foils the times in minutes for the conversion of 5–6 mg. of potassium in 50 ml. of liquid ammonia to amide are: platinized platinum, 2.6; rusted iron, 3.1; nickel, 21; pure iron, 44; smooth platinum, 66; zinc, 71–86; copper, 102–232; silver, 245–252; gray platinum, 556; tantalum and niobium, 1000; no catalyst, 1500. The effect of stirring was also determined. The time of reaction was found to increase markedly with a decrease in the rate of stirring below 200 R.P.M. The relative order for powdered catalysts was the same. It was found that the product formed, potassium amide, had little or no effect upon the activity of the catalyst even when present in high concentration. The presence of sodium amide, however, seems to poison the catalyst.

Juza and coworkers (41) studied the preparation of the alkali amides. For 1–2 g. of metal in about 40 ml. of liquid ammonia at room temperature in the presence of a platinized platinum gauze as a catalyst the following times were required for complete reaction: lithium, 7–8 days (23 on one occasion); sodium, 6–8 days (12 on one occasion); potassium, 2 hr.; rubidium and cesium, 0.5 hr. The velocity of sodium amide formation from a liquid ammonia solution of sodium in a stainless-steel vessel at room temperature has been roughly measured by the increase in pressure. The results are not strictly reproducible and appear to depend upon the previous treatment of the vessel and other factors difficult of control. The activation energy of the reaction is given as 10.7 kcal. (2).

The preparation of potassium amide free of metal oxide particles etc. has been described (65). A solution of potassium in liquid ammonia is converted to the amide, using a solid single-unit catalyst, and the resulting solution of amide is filtered, evaporated, and pulverized.

The production of alkali amides by the electrolysis of salt solutions in liquid ammonia has been extensively investigated (5, 6, 7, 87, 93). For the electrolysis of chlorides, bromides, and nitrates of the alkali metals, Akhumov (5) provides a cell, the cathode of which is a perforated iron cylinder with a solid bottom.

This cylinder is surrounded by anodes whose inner surfaces come into contact with a diaphragm, the lower end of which is attached to a solid disk placed below the bottom of the cathode.

The electrolysis of potassium bromide in liquid ammonia was carried out successfully by Akhumov and Druzyakova (7), using 6–10 v. Yields of 80–99 per cent of potassium amide were obtained.

$$6KBr + 14NH_3 \rightarrow 6NH_4Br + 6KNH_2 + 3H_2 + N_2$$

Silsby (87) describes an apparatus and a method of operation which involves maintaining between the anode and cathode a liquid partition of an alkali metal salt solution. A gradual flow of the solution through the space between the anode and cathode is maintained at a rate sufficient to prevent migration of alkali metal to the anode.

The alkali amides are often formed as by-products of the reducing action of the alkali metals in liquid ammonia. These reactions can be found readily elsewhere (95, 96).

The preparative methods which have been used for the alkali amides have been reviewed by Juza (40, 41).

Lithium imide may be obtained by the careful thermal decomposition of lithium amide. It is essential that melting of the amide and decomposition of the imide be avoided. These objectives are accomplished by heating the amide to 360°C. in a high vacuum until the evolution of ammonia is almost complete and then slowly raising the temperature to 450°C. (46).

V. PROPERTIES OF THE ALKALI AMIDES

Juza and coworkers have made a very careful study of the metal amides and nitrides. The physical properties of the alkali amides are listed in table 1 (41). On the basis of the heat of formation of the amides of the metals of group I, Juza (40) has discussed the energy relations of these amides and compared them to hydroxides and oxides. Also, he has discussed the structure of the amides on the basis of their melting points, molecular volumes, and electrical conductance. The proton affinity of the NH_2 group for the different metals ranges from 337 to 380. The crystal structure of lithium amide has been determined (45). The sub-

TABLE 1

Physical properties of the alkali amides

AMIDE	MELTING POINT	DENSITY $d_{4^\circ}^{25^\circ}$	HEAT OF SOLUTION	HEAT OF FORMATION
	°C.		*kcal./mole*	*kcal./mole*
$LiNH_2$	373–375	1.18	56.3 ± 0.2	42
$NaNH_2$	208	1.39	61.4 ± 0.05	27
KNH_2	338	1.64	64.9 ± 0.15	27
$RbNH_2$	309 ± 1	2.58	66.4 ± 0.1	26
$CsNH_2$	262 ± 1	3.43	67.0 ± 0.2	28

stance is tetragonal with the lattice constants $a = 5.016$ Å., $c = 10.22$ Å. There are 8 $LiNH_2$ in the unit cell and the space group is S_4^2 (figure 1).

Sigetomi (86) investigated the solubility of sodium amide in liquid ammonia at different temperatures and found its solubility per 100 g. of ammonia to be as follows: 20°C., 0.16_3 g.; 10°C., 0.14_9 g.; 0°C., 0.14_0 g.; −10°C., 0.13_0 g.; −20°C., 0.11_4 g. An investigation of the ternary system $NaNH_2$–NaCl–NH_3 over a temperature range of −20°C. to 20°C. disclosed the fact that the solubility of sodium amide or sodium chloride in liquid ammonia increased greatly with addition of sodium chloride or sodium amide, respectively. The transition point of sodium

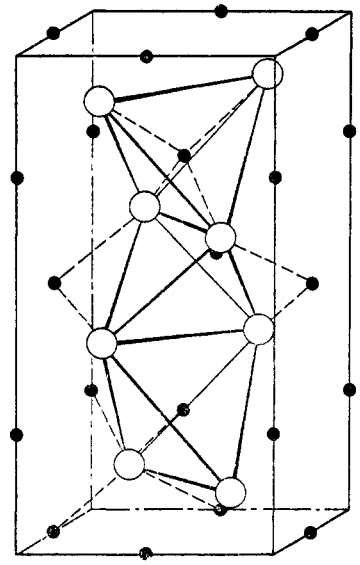

FIG. 1. Unit cell of lithium amide: ●, Li; ○, NH_2

chloride in liquid ammonia was not altered appreciably by the coexistence of sodium amide.

A liquid ammonia solution of potassium amide absorbs light in the near ultraviolet and thereby becomes photoconducting, presumably owing to the liberation of electrons (62).

$$NH_2^-(NH_3) + h\nu \rightarrow NH_2(NH_3) + e^-(NH_3)$$

Since no overall photochemical reaction is observed, the recapture of conduction electrons by the free amide radicals must be rapid.

Liquid ammonia solutions of potassium amide effect the ortho–para hydrogen conversion and also exchange with deuterium gas even at −50°C. A 0.001 M solution of potassium amide has a half-life of < 1 min. for the exchange in solution. The molar rate constant appears to increase with dilution, a fact which suggests that the amide ion is the catalytic species (26).

The thermal decomposition of sodium amide has been studied by Sakurazawa

and Hara (70), who examined the decomposition products of sodium amide through the temperature range of 335–400°C. The following equations are believed to express the decomposition mechanism:

$$NaNH_2 \rightarrow NaH + 0.5N_2 + 0.5H_2 \quad (1)$$

if the total gas pressure is kept above the decomposition pressure of sodium hydride.

$$NaNH_2 \rightarrow Na + 0.5N_2 + H_2 \quad (2)$$

if the gaseous products are pumped away and the pressure is kept below the decomposition pressure of sodium hydride.

$$NaNH_2 + H_2 \rightarrow NaH + NH_3 \text{ (a side reaction)} \quad (3)$$

The occurrence of free sodium amide in the universe has been postulated on the basis of data obtained from a spectroscopic study of the atmosphere of the planet Jupiter (101). The colored bands in Jupiter's atmosphere are attributed to the formation of solutions of sodium in ammonia, which are reddish brown in color at temperatures above −112°C. The yellowish tints which are present are attributed to sodium amide, formed by the slow decomposition of the solution of sodium in ammonia.

Lithium imide (d = 1.48) is isomorphous with lithium oxide (antiisomorphic with calcium fluoride) and has a lattice constant of 5.04_7 Å. It forms no ammoniate at low temperatures (46).

VI. DETERIORATION OF THE AMIDES DURING STORAGE

The widespread use of the alkali amides in organic syntheses has provided a large number of chemists with experience in handling the alkali amides. With this experience, the formerly prevalent fear of the alkali amides has largely disappeared. Occasionally one hears of an explosion of a sample of alkali amide, but the cause can always be traced to improper handling. The case reported by Shreve *et al.* (85) remains as the only exception to this statement.

The physiological effects resulting from acute exposure to sodium amide have been reported (66).

VII. ANALYSIS OF THE AMIDES AND THEIR REACTION PRODUCTS

When studying reactions in the molten amides, it often becomes necessary to hydrolyze a sizable amount of the solid amide prior to analysis of other constituents in the melt. This can be accomplished best by cooling the reaction vessel in ice, covering the amide with toluene, and then adding water drop by drop to the vigorously stirred toluene mixture (71).

VIII. THE NATURE OF THE FUSED AMIDES

The presence of sodium hydride in sodium amide which has been prepared by the interaction of ammonia with molten sodium has been recognized for some time (17). This is especially true if the reaction is conducted at a comparatively

low temperature (<250°C.) or if ammonia has not been bubbled through the molten material for some time after all of the sodium has disappeared. Now it is known that some small amount of sodium hydride is probably present in all sodium amide prepared from ammonia gas and molten sodium or in any sample which has been melted (71). Sodium amide decomposes to some extent according to the equation

$$2NaNH_2 \rightleftharpoons 2NaH + N_2 + H_2$$

However, if ammonia is passing through the molten amide, the hydride is reconverted to amide.

$$2NaH + 2NH_3 \rightleftharpoons 2NaNH_2 + 2H_2$$

The net result is an apparent "cracking" of the ammonia:

$$2NH_3 \rightleftharpoons N_2 + 3H_2$$

Ammonia passed through molten sodium amide contains nitrogen and hydrogen at temperatures much below those at which ammonia alone would be "cracked" and at higher temperatures in greater quantity than would have resulted from thermal "cracking" alone. The rate of this cracking is considerably influenced by the presence of other materials in contact with or dissolved in the amide. Solid molybdenum and rhenium powder increased the rate of "cracking" by factors of 1.4 and 3.3, respectively. The reaction products of lanthanum and cerium increased the rate of "cracking" (1.9 and 1.2, respectively), whereas those of tin decreased the rate (0.63) (19).

That the decomposition of sodium amide is reversible can be shown by varying the rate of flow of ammonia through the amide. If the rate of flow is increased from a value previously held until the nitrogen and hydrogen in the gaseous effluent are in the ratio 1:3, the rate of nitrogen production increases rapidly. A change in the rate of flow cannot alter the rate of decomposition, but it can remove the gaseous decomposition products and establish a new equilibrium where more sodium hydride is present than was true previously. It is entirely possible that the sodium hydride present in sodium amide will affect the reaction of the molten (or solid) amide. This would be especially true if reactions were being conducted in an inert atmosphere (flowing) or if an inert carrier gas were being used to conduct a volatile material through the molten amide (31). Much work is needed to establish the effects of the sodium hydride upon the reactions of sodium amide.

IX. REACTIONS OF THE ELEMENTS WITH THE ALKALI AMIDES

Most of the reactions listed below are those for the molten amides. For such reactions the water-insoluble gases evolved may be readily obtained. However, it is difficult to obtain *direct* information as to the nature of the reaction products because of the necessity of hydrolyzing the melt prior to analysis. The products of the reaction are usually altered during the hydrolysis of the amide. If potassium amide is used in place of sodium amide, the resulting product may be ex-

tracted with liquid ammonia and any insoluble product isolated. However, the separation of a soluble product from an excess of soluble potassium amide is usually not possible. These limitations of experimental techniques must be kept in mind in what follows.

Group I, Subgroup A

Hydrogen: The preparation of sodium hydride by treating molten sodium amide with hydrogen at a temperature not exceeding 200°C. is the subject of a recent patent. The hydride obtained is extracted from unchanged amide with liquid ammonia (8). Apparently the temperature of the ammonia must be kept very low, because sodium hydride reacts rapidly with liquid ammonia at 20°C. and slowly at −40°C. (68).

Group III, Subgroup A

Lanthanum: Molten sodium amide (350°C.) attacks lanthanum filings (98 per cent lanthanum) fairly rapidly to liberate hydrogen gas (H:La = 3) (19).

Cerium: Molten sodium amide (350°C.) reacts slowly with cerium filings to liberate hydrogen (H:Ce somewhat less than 2) (19).

Group III, Subgroup B

Indium: Unlike aluminum, indium with an amalgamated surface is not acted upon by a solution of potassium amide in liquid ammonia (88). Even molten sodium amide (350°C.) does not attack indium (4.5 hr.) (19).

Group IV, Subgroup A

Thorium: Molten sodium amide (350°C.) and thorium (small pieces) react very slowly with the liberation of a small amount of hydrogen (19).

Group IV, Subgroup B

Carbon: Recent patents cover the production of cyanides by the reaction of an alkali metal amide, or alkali metal and ammonia, with carbon prepared by carbonizing coal at 450–650°C. (23, 24).

Silicon: Molten sodium amide (350°C.) acts slowly on finely divided silicon to liberate hydrogen (19). Potassium amide (375–400°C.) also attacks silicon slowly, with the production of a small amount of an amorphous white material which is insoluble in liquid ammonia and is presumably potassium ammonosilicate (29).

Germanium: Molten sodium amide (350°C.) and finely divided germanium react readily with the liberation of hydrogen (H:Ge = approximately 3) (19).

Tin: Molten sodium amide (350°C.) and tin react with the evolution of a small amount of nitrogen. The recovery of metallic tin upon hydrolysis of the melt indicates the formation of a stannide during the reaction (19).

Tin reacts vigorously (evolution of very little gas) with molten potassium amide (375–400°C.) to form a dark brown homogeneous melt. All of the products are soluble in liquid ammonia. The coloring matter of the resulting red-brown

solution is extracted by mercury. A soluble tin compound remains dissolved in the ammonia, indicating that the reaction follows essentially the same course with molten amides as with their liquid ammonia solutions (29).

Lead: Molten sodium amide (350°C.) reacts slowly with lead to liberate a small amount of nitrogen (19). The reaction of lead with molten potassium amide (375–400°C.) gives very little gas and a colored melt which is entirely soluble in liquid ammonia. From the resulting dark brown solution, the coloring matter can be removed by mercury. Presumably a polyplumbide other than K_4Pb_9, whose solution is deep green in color, is formed. Lead remains in the solution after extraction of the polyplumbide, presumably as potassium ammonoplumbite (29).

Group V, Subgroup A

Niobium: Molten sodium amide (350°C.) reacts very slowly with niobium powder (98 per cent) to liberate a small amount of nitrogen (19).

Tantalum: Molten sodium amide (350°C.) shows no reaction with tantalum powder in 4 hr. (19).

Group V, Subgroup B

Phosphorus: Red phosphorus reacts vigorously with molten sodium amide (350°C.) to evolve hydrogen (H:P = approximately 4) (19).

Red phosphorus and molten potassium amide (375–400°C.) react vigorously to liberate hydrogen. The initial red color of the melt (polyphosphide?) gradually disappears as the reaction proceeds. At the end of the reaction, a gray ammonia-insoluble product is obtained which approximates potassium ammonophosphite, $P(NHK)NK \cdot NH_3$, in composition (29). The action of molten potassium amide (400°C.) on potassium polyphosphide yields the same gray substance as that obtained with phosphorus (38).

A liquid ammonia solution of potassium amide (room temperature) reacts with red phosphorus to give a deep red solution and a light brown insoluble material. Repeated washing with ammonia does not yield colorless washings. The solid product remaining appears to be an ammonophosphite, P(NH)NHK, contaminated with other products, probably phosphides or an ammonohypophosphite (37). Lithium amide and red phosphorus react in liquid ammonia to form a dark red-brown solution which separates into two liquid phases as the reaction proceeds. Attempts to separate any definite reaction products were unsuccessful (30).

Arsenic: The reaction of molten sodium amide (350°C.) on arsenic is accompanied by the evolution of a small amount of nitrogen (probably owing to decomposition of an ammonoarsenite). The finely divided precipitate of arsenic in the products of hydrolysis of the melt indicates that a polyarsenide is formed (19). Arsenic and molten potassium amide (375–400°C.) react with the formation of very little gas. The red-brown melt contains polyarsenide and some other ammonia-soluble arsenic compound (29).

Antimony: Molten sodium amide (350°C.) reacts slowly with antimony powder

to evolve nitrogen (Sb:N = approximately 2). The hydrolysis products indicate formation of antimonides (18). Molten potassium amide (375–400°C.) reacts readily with antimony. Nitrogen is evolved and the red melt contains polyantimonides (29). A liquid ammonia solution of potassium amide reacts slowly with pulverized antimony to form a deep red-brown solution and a white precipitate. Apparently the reaction is

$$(x + 1)\mathrm{Sb} + 4\mathrm{KNH_2} \rightarrow \mathrm{Sb(NH_2)NK} + \mathrm{K_3Sb}_x + 2\mathrm{NH_3}$$

with the value of x near 7, and the insoluble product is contaminated with $\mathrm{Sb(NH)NK_2}$ (91).

Bismuth: Molten sodium amide (350°C.) reacts slowly with finely divided bismuth to liberate nitrogen in an amount corresponding to the equation (19):

$$2\mathrm{Bi} + 6\mathrm{NaNH_2} \rightarrow 2\mathrm{Na_3Bi} + \mathrm{N_2} + 4\mathrm{NH_3}$$

Molten potassium amide (375–400°C.) rapidly attacks bismuth with the evolution of nitrogen and the formation of a dark purple melt. Extraction of the latter with liquid ammonia gives a solid which consists of a mixture of $\mathrm{K_3Bi}$ and $\mathrm{K_3Bi_2}$ (29).

Group VI, Subgroup A

Molybdenum: Both molybdenum powder and fine wire are acted upon very slightly, if at all, by molten sodium amide (350°C.) (19). Molten potassium amide (400°C.) does not attack molybdenum wire to any noticeable extent (5 hr.) (38). Molten potassium amide (375–400°C.) slowly attacks small lumps of molybdenum to form a small amount of an orange-brown material which is insoluble in liquid ammonia. This material contains molybdenum, potassium, and nitrogen, but is variable in composition (29).

Tungsten: Small lumps of tungsten do not react with molten sodium amide (350°C.), while tungsten powder reacts slightly with the evolution of a small amount of hydrogen (19). Molten potassium amide (400°C.) does not attack small pieces of a tungsten wire to any noticeable extent (5 hr.) (38). Molten potassium amide (375–400°C.) slowly attacks small lumps of tungsten to form a small amount of a yellow material which is insoluble in liquid ammonia. This product contains tungsten, potassium, and nitrogen, but it is variable in composition (29).

Group VI, Subgroup B

Oxygen: Pure oxygen and oxygen in the air react readily with molten sodium amide to form nitrogen. At 250°C. the amount of nitrogen corresponds to within 5 per cent of that expected from the equation

$$6\mathrm{NaNH_2} + 3\mathrm{O_2} \rightarrow 6\mathrm{NaOH} + 2\mathrm{N_2} + 2\mathrm{NH_3}$$

At higher temperatures the amount of nitrogen is less than that called for in the equation. Oxygen and molten potassium amide react similarly, but because of the higher melting point of potassium amide, the reactions cannot be con-

ducted below 350°C. The nitrogen discrepancy from the equation is 5–10 per cent at 350°C. and 10–12 per cent at 395°C. (18, 19, 71).

The oxidation of potassium amide by dry oxygen is explained by the formation of $KONH_2$ and K_2O_4. The K_2O_4 forms a protective layer, which retards the reaction, and by diffusion the K_2O_4 reacts with KNH_2 to give KNO_2 and KOH. A maximum of yellow coloration occurs at the end of the reaction (52).

Sulfur: Molten sodium amide (250–340°C.) reacts with sulfur to evolve nitrogen. The rate of nitrogen evolution increases as the temperature is increased (19). Molten potassium amide (375–400°C.) attacks sulfur vigorously to liberate nitrogen gas. On extracting the melt with liquid ammonia potassium sulfide was obtained (29).

Selenium: The rapid reaction between molten sodium amide (255°C.) and selenium is accompanied by the evolution of nitrogen (19). Molten potassium amide (375–400°C.) and selenium react vigorously to form nitrogen and potassium selenide. The latter is obtained by extracting the melt with liquid ammonia (29).

Tellurium: Molten sodium amide (350°C.) reacts readily with tellurium to evolve nitrogen in agreement with the equation:

$$3Te + 6NaNH_2 \rightarrow 3Na_2Te + N_2 + 4NH_3$$

The deep purple color of the hydrolysis solution indicates the presence of a small amount of polytelluride (19). Tellurium and excess molten potassium amide (375–400°C.) react vigorously with evolution of nitrogen. Potassium telluride and some polytelluride have been identified in the melt (29).

Group VII, Subgroup A

Rhenium: Molten sodium amide (350°C.) does not react with rhenium powder (20).

Group VIII

Platinum: Both platinum wire and platinum powder are attacked only slightly by molten sodium amide (350°C.) to liberate a small amount of nitrogen (19).

X. REACTIONS OF THE ALKALI AMIDES WITH COMPOUNDS

Hydrides: Germane and potassium amide react in liquid ammonia at −33°C. to give $KGeH_3$, together with a small amount of an unknown material produced by a side reaction (32). The compound $KGeH_3$ reacts with potassium amide with the evolution of large amounts of hydrogen (47, 90). Trimethylstannane reacts with potassium amide in liquid ammonia according to the equation:

$$(CH_3)_3SnH + KNH_2 \rightarrow (CH_3)_3Sn^-K^+ + NH_3$$

With triethylsilane, reaction proceeds according to the equation:

$$2(C_2H_5)_3SiH + KNH_2 \rightarrow [(C_2H_5)_3Si]_2\,NK + 2H_2$$

It would be interesting to establish the nature of the reaction between triethylgermane and potassium amide (48).

Dimethylphosphine forms an orange complex with amide ion (from sodium

amide) in liquid ammonia. This complex liberates hydrogen and the resulting salt yields bis(dimethylphosphino)amine, $[(CH_3)_2P]_2NH$, upon treatment with ammonium bromide (94). The reaction

$$KNH_2 + AsH_3 \rightarrow KAsH_2 + NH_3$$

has been carried out in liquid ammonia at −78°C. (39). The arsine can be regenerated by treating the yellow solution of dihydrogen arsenide with ammonium bromide.

$$KAsH_2 + NH_4Br \rightleftharpoons AsH_3 + KBr + NH_3$$

Oxides: Germanium dioxide is not acted upon by a liquid ammonia solution of potassium amide at room temperature (99). Hexamethyldisiloxane reacts with sodium amide in liquid ammonia according to the following equation (35, 36):

$$2[(CH_3)_3Si]_2O + 2NaNH_2 \rightarrow 2(CH_3)_3SiONa + [(CH_3)_3Si]_2NH + NH_3$$

Potassium amide reacts in an analogous fashion in ether.

Additional patents covering the manufacture of alkali azides by the reaction of nitrous oxide with molten alkali amides have appeared (54, 55, 56). Another patent (100) covers the extraction of sodium azide from the reaction product by means of liquid ammonia. In a careful study of the formation of sodium azide in liquid ammonia at room temperature by the reactions

$$4Na + 3N_2O + NH_3 \rightarrow NaN_3 + 3NaOH + 2N_2$$

$$N_2O + 2NaNH_2 \rightarrow NaN_3 + NaOH + NH_3$$

it was established that the first reaction proceeds through the intermediate formation of sodium amide (3). In the first reaction the rate of formation is rapid and the yield nearly 100 per cent; in the second, where the sodium is first converted to the amide, the utilization of the sodium is more effective but the rate of formation is slower and the yield is more than 95 per cent (1). A patent has been issued for the preparation of sodium azide by the reaction between nitrous oxide and sodium amide in liquid ammonia (4).

Sodium amide and nitrogen dioxide in carbon tetrachloride produce a mixture of $Na(NH_2N_2O_3)$ and $Na(NH_2N_2O_5)$. The reaction is vigorous and is accompanied by the emission of sparks. Under the same conditions sodium amide and chlorine dioxide form sodium amidochlorate. Sodium amide and iodine pentoxide in liquid ammonia form the sodium salt of sodium amidoiodic acid (11).

Potassium amide in liquid ammonia solution at room temperature reacts with BiOI to form the dark red, explosive solid, $BiONH_2$ (98).

Cyanides: Sodium cyanide (C^{14}-labelled) was obtained in high yields (usually > 85 per cent) by heating sodium formate with two molecular proportions of sodium amide at 620°C. for 2 min. in a steel bomb (89).

Carbonates: Barium amide and C^{14}-labelled barium carbonate heated to dull redness produce C^{14}-labelled barium cyanamide, from which C^{14}-labelled urea can be obtained (59).

Nitrates: Bergstrom (13, 16) found that liquid ammonia solutions of potas-

sium nitrate and potassium amide in the presence of certain oxide catalysts interact slowly according to the equation:

$$3KNH_2 + 3KNO_3 \rightarrow 3KOH + N_2 + NH_3 + 3KNO_2$$

With the best catalysts the reaction may be complete in 5–7 days, whereas with others several months may be required. The catalysts are as follows: particularly good, Fe_2O_3, Co_2O_3, NiO; fairly effective, CuO and Mn_3O_4; very poor, ZnO, Al_2O_3; weak, KOH. Iron wire has very little influence. Azide is not formed (or it is formed only in traces) in catalyzed reactions at room temperature, although it is obtained at higher temperatures when the catalyst is omitted.

Nitrites: Potassium nitrite reacts at an extremely slow rate with a liquid ammonia solution of potassium amide at room temperature and in the presence of Fe_2O_3 or Co_2O_3 according to the equation (16):

$$KNO_2 + KNH_2 \rightarrow 2KOH + N_2$$

With molten potassium amide (255°C.), however, the reaction is vigorous. At higher temperatures (350°C.), a much smaller quantity of nitrogen than expected is obtained (18).

Permanganates: Potassium permanganate is reduced by potassium amide in liquid ammonia solution at −33°C. (51).

$$6KMnO_4 + 6KNH_2 \rightarrow 6K_2MnO_4 + 4NH_3 + N_2$$

Alkoxides: Aluminum ethoxide, $Al(OC_2H_5)_3$, reacts with potassium amide in liquid ammonia to form soluble $[(C_2H_5O)_3AlNH_2]$ (73, 77). Under the same conditions, titanium ethoxide forms insoluble $K_2[(C_2H_5O)_4Ti(NH_2)_2]$.

Trialkylgallium: Two molecules of trimethylgallium ammine react with one molecule of sodium amide to form bis(trimethylgallium)-sodium amide (49).

$$NaNH_2 + 2(CH_3)_3Ga \cdot NH_3 \rightarrow NaNH_2(Ga(CH_3)_3)_2 + 2NH_3$$

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Part II. Alkali Amides as Reagents for Organic Reactions

ROBERT LEVINE

CONTENTS

I. Introduction

This part of the review is concerned with the uses of the alkali amides in organic chemistry which have appeared in the literature from 1937 through 1952.

In bringing the chemistry of the alkali amides up to date (83, 84), it is probable that a number of references have been omitted because of the difficulty of finding many of the articles which deal only incidentally with this subject.[1] Therefore, the author sincerely hopes that omissions will be brought to his attention.

The arrangement of the material in the present review is somewhat different from that in the earlier reviews (83, 84). The reaction of two organic compounds in the presence of an alkali amide may be classified under either compound. To facilitate the location of material included in this review, the following scheme has been adopted. *The reaction between any two compounds and an alkali amide will be discussed under that compound which is converted to its anion by the alkali amide.* For example, while in the earlier reviews the reactions of ketones with esters to give β-diketones are listed under esters, in the present paper these reactions are found under ketones, since the ketones are converted to their anions by the alkali amides.

II. Preparation of Organic Analogues of the Alkali Amides

The organic analogues of the alkali amides are prepared by acid–base reactions in which amines are metalated by alkali amides and sodium or lithium alkyls or aryls. Thus, lithium diethylamide (340) has been prepared by the

$$R_2NH + LiR' \rightarrow R'H + R_2NLi$$

reaction of methyllithium with diethylamine; and Horning and Bergstrom (427), using Ziegler's method (*cf.* 84, page 429), have prepared lithium diethylamide and di-*n*-butylamide by the reaction of phenyllithium with the corresponding secondary amines. Lithium diethylamide and lithium ethylphenylamide have been obtained by the interaction of lithium, naphthalene, and the secondary amines (905). Presumably the naphthalene is converted to a lithium derivative, which then reacts with the amines.

There are numerous examples in the literature in which amines have been metalated with sodium amide and the resulting sodium derivatives have then been alkylated, arylated, or "heterylated."[2] These reactions will be discussed in later sections of this review.

III. Hydrocarbons

A. Olefins

The metalation of allylic hydrocarbons with sodium amide and the reactions of these sodium derivatives have been studied intensively. Campbell and Young (181) found that the reaction of both allyl- and propenylbenzene with sodium

[1] Most of the references were obtained by a page-by-page scanning of *Chemical Abstracts*. The author expresses his gratitude to N. N. Goldberg, T. F. McGrath, C. Osuch, H. E. Reich, M. L. Swicklick, and C. W. Yoho for their assistance.

[2] The term "heterylate" is used in this review to designate a process by which a heterocyclic radical, e.g., 2-furyl, 2-pyridyl, or 2-thienyl, is introduced into an organic ompound in place of a hydrogen atom. In heterocylic chemistry "heterylation" has a meaning comparable to that associated with alkylation and arylation in the chemistry of aliphatic and aromatic compounds, respectively.

amide in liquid ammonia and subsequent treatment of the reaction mixtures with the proton donors methanol, ammonium ion, or phenylacetylene gave predominantly propenylbenzene. These results may be explained by assuming that both olefins give rise to the same resonating system of carbanions and that the primary carbanion is more reactive than the secondary carbanion towards proton donors.

$$RCH_2CH{=}CH_2 \text{ and/or } CH_3CH{=}CHR \xrightarrow{NaNH_2}$$

$$[R\ddot{C}HCH{=}CH_2 \leftrightarrow RCH{=}CH\ddot{C}H_2]^- Na^+$$

Secondary carbanion AII — Primary carbanion AI

$$\downarrow$$

AI,II

$$AI \xrightarrow{CH_3OH,\ NH_4^+,\ \text{or } RC{\equiv}CH} RCH{=}CHCH_3$$

R = C_6H_5.

In extending this work (182), sodioallylbenzene (AI,II) has been carbonated and treated with acetone and benzophenone. Only one compound, diphenylcinnamylcarbinol (75 per cent), was isolated from the benzophenone reaction. This alcohol arises from the reaction of AI with benzophenone. However, in the carbonation and acetone reactions apparently both carbanions AI and AII react, since a pair of isomeric compounds is isolated from each reaction. In the

$$AI,II + CH_3COCH_3 \rightarrow \underset{(35\%)}{RCH{=}CHCH_2C(CH_3)_2OH} + \underset{\displaystyle C(CH_3)_2OH}{\underset{|}{RCHCH{=}CH_2}}\ (65\%)$$

R = C_6H_5.

reactions of sodioallylbenzene with α-halogenated aliphatic esters, mixtures of isomeric alkylated compounds were also obtained (183). While the alkylation of AI,II with allylic halides (557) has been reported to give only products derived from AII, a more recent study (901) of these reactions has revealed that both AI and AII are alkylated but that the major product arises from the alkylation of the secondary carbanion, AII.

Cyclopentadiene (357) has been alkylated with alkyl bromides, alkyl sulfates, and allylic chlorides to mixtures of compounds in which the 2-alkyl derivatives predominate. A number of other cyclic dienes have been alkylated (102, 107). Thus, 1,5-dimethoxy-1,4-cyclohexadiene, when treated with 2-phenylethyl bromide and potassium amide in liquid ammonia, gives 1,5-dimethoxy-6-(2-phenylethyl)-1,4-cyclohexadiene (107).

The hydrogenation of 2,6-dimethyl-3,5-octadiene (268) in the presence of sodium amide, which gives a mixture of the *cis*- and *trans*-2,6-dimethyl-4-octenes, apparently involves a 1,4-hydrogenation of the conjugated olefinic system accompanied by bond isomerization. A number of cyclic dienes containing isolated double bonds have been converted to isomeric compounds containing conjugated double bonds when treated with alkali amides (101). Thus, 1-methoxy-1,4-cyclohexadiene (2,5-dihydroanisole) is isomerized to 1-methoxy-

1,3-cyclohexadiene (2,3-dihydroanisole) when treated with potassium amide in liquid ammonia solution.

The mechanism for the polymerization of monomers such as styrene, methyl methacrylate, and acrylonitrile by the alkali amides has been discussed (282, 411, 746) and involves the following three steps.

$$NH_2^- + RCH{=}CH_2 \rightarrow R\bar{C}HCH_2NH_2 \qquad \text{Initiation}$$

$$R\bar{C}HCH_2NH_2 + xRCH{=}CH_2 \rightarrow NH_2(CH_2CHR)_x^- \qquad \text{Propagation}$$

$$NH_2(CH_2CHR)_x^- + NH_3 \rightarrow NH_2(CH_2CHR)_xH + NH_2^- \qquad \text{Termination}$$

R = C_6H_5.

trans-1,2-Diethoxyethylene is converted to the sodium derivative of ethoxyacetylene when treated with sodium amide (752).

B. ACETYLENES

1. Alkylation reactions

Sodium and lithium acetylide and some of their substituted derivatives, prepared by the reaction of acetylene or the monosubstituted acetylenes with sodium amide or lithium amide in liquid ammonia, have been alkylated with the following classes of reagents: alkyl halides (132, 133, 177, 281, 406–8, 573, 587, 651, 682, 858), dihaloalkanes (8, 9, 439, 538, 657, 658, 717, 842), haloepoxides (396, 399), dialkyl sulfates (218, 406, 549, 550, 858, 867), and acetals (520). Since the alkylation of the metallic derivatives of acetylene was thoroughly reviewed in 1949 by Jacobs (456), only a few examples of the most recent work will be discussed.

Acetylene has been dialkylated with *n*-octyl bromide in the presence of lithium amide in liquid ammonia solution to give 9-octadecyne in 41 per cent yield and lithio-*n*-amylacetylene has been alkylated with *n*-undecyl bromide to give 6-octadecyne in 76 per cent yield (281). 1-Pentyne has been methylated with dimethyl sulfate to give 2-hexyne in 60 per cent yield (549).

$$n\text{-}C_3H_7C{\equiv}CH \xrightarrow[(2)\ (CH_3)_2SO_4]{(1)\ NaNH_2} n\text{-}C_3H_7C{\equiv}CCH_3$$

A recent synthesis of vaccenic acid (*trans*-11-octadecenoic acid) involves the alkylation of 1-octyne with 1-chloro-9-iodononane (8).

$$CH_3(CH_2)_5C{\equiv}CH + I(CH_2)_9Cl \xrightarrow{NaNH_2} CH_3(CH_2)_5C{\equiv}C(CH_2)_9Cl \quad (93.5\%)$$

$$CH_3(CH_2)_5C{\equiv}C(CH_2)_9Cl \xrightarrow[(3)\ H_2,\ Ni]{(1)\ NaCN;\ (2)\ NaOH,\ H_2O;\ H^+} CH_3(CH_2)_5\underset{H}{\overset{H}{C{=}C}}(CH_2)_9COOH$$

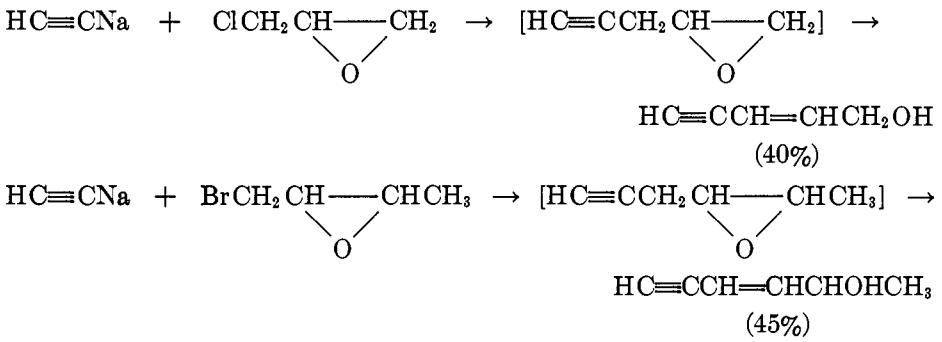
cis-11-Octadecenoic acid (74%)

$$CH_3(CH_2)_5\underset{H}{\overset{H}{C{=}C}}(CH_2)_9COOH \xrightarrow{Se,\ 180\text{–}200^\circ C.} CH_3(CH_2)_5\underset{H}{\overset{H}{C{=}C}}(CH_2)_9COOH$$

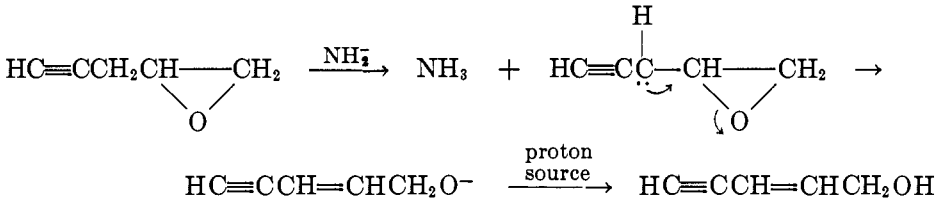
Vaccenic acid (46.2%)

1-Heptyne has been alkylated with acetaldehyde diethyl acetal (520) to give 2-ethoxy-3-nonyne (4 per cent).

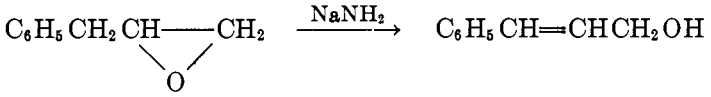
The sodium derivatives of acetylene, phenylacetylene, and *n*-butylacetylene have been alkylated with epichlorohydrin to give enynols; and sodium acetylide was alkylated with 1-bromo-2,3-epoxybutane to give a 45 per cent yield of 3-hexen-5-yn-2-ol (396, 399).



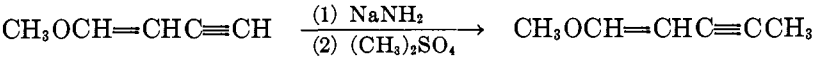
These unsaturated alcohols are believed to be formed by rearrangement of the intermediate acetylenic epoxides. A possible course for such rearrangements is indicated below.



While none of the intermediate acetylenic epoxides were isolated in the above reactions, it was shown that epoxides will rearrange to unsaturated alcohols when treated with sodium amide. Thus, cinnamyl alcohol is obtained in 80 per cent yield when 3-phenylpropylene oxide is treated with sodium amide (396).



1-Methoxy-1-buten-3-yne (395) has been alkylated by dimethyl sulfate (60 per cent yield) and diethyl sulfate (15 per cent yield).



2. Acylation, carbonation, and carbethoxylation reactions

Fuson and Meek (299) have acylated the sodium derivative of mesitylacetylene with mesitoyl chloride and obtained a 40–60 per cent yield of mesitoylmesitylacetylene.

Acetylenic alcohols have been carbonated (663, 713) to give hydroxyacetylenic acids. Thus, the reaction of 3-hydroxy-3-phenylpropyne with sodium amide and carbon dioxide gives 4-hydroxy-4-phenyl-2-butyn-1-oic acid.

Zoss and Hennion (908) have prepared a number of acetylenic acids by the following scheme, where R is an alkyl radical. Thus, 2-pentynoic acid (49 per cent yield) and 2-hexynoic acid (42 per cent yield) were obtained.

$$RC{\equiv}CH \xrightarrow[(3)\ NaHSO_4]{(1)\ NaNH_2,\ (2)\ CO_2} RC{\equiv}CCOOH$$

Carbonation of a mixture of the mono- and disodium salts (536), obtained from the reaction of 1,9-decadiyne with sodium amide, gives a mixture of 1,9-decadiyne-1-carboxylic acid and 1,9-decadiyne-1,9-dicarboxylic acid.

$$HC{\equiv}C(CH_2)_6C{\equiv}CH \xrightarrow[(2)\ CO_2]{(1)\ NaNH_2} HC{\equiv}C(CH_2)_6C{\equiv}CCOOH \text{ and } HOOCC{\equiv}C(CH_2)_6C{\equiv}CCOOH$$

Acetylene and phenylacetylene have been treated with sodium amide and diethyl carbonate (243–245). Although it might be expected that these reactions would merely involve the replacement of the acetylenic hydrogen atoms by carbethoxyl groups, as was observed earlier by Levine and Hauser (553) when ketones were treated with diethyl carbonate in the presence of sodium amide, this was not the case. Thus, the reaction of acetylene and diethyl carbonate gave the four products ethyl β-ethoxyacrylate (I), ethyl β,β-diethoxypropionate (II), ethyl ethoxymaleate (III), and ethyl α,α-diethoxysuccinate (IV), while the reaction of phenylacetylene and diethyl carbonate gave ethyl β-ethoxy-β-phenylacrylate (V) and ethyl β,β-diethoxy-β-phenylpropionate (VI).

$$HC{\equiv}CH + (C_2H_5O)_2CO \xrightarrow{NaNH_2,C_2H_2,NH_3}$$

$C_2H_5OCH{=}CHCOOC_2H_5$ (I) $\quad (C_2H_5O)_2CHCH_2COOC_2H_5$ (II)

$C_2H_5OOCC(OC_2H_5){=}CHCOOC_2H_5$ (III) $\quad C_2H_5OOCC(OC_2H_5)_2CH_2COOC_2H_5$ (IV)

$$C_6H_5C{\equiv}CH + (C_2H_5O)_2CO \xrightarrow{NaNH_2,NH_3}$$

$C_6H_5C(OC_2H_5){=}CHCOOC_2H_5$ (V) and $C_6H_5C(OC_2H_5)_2CH_2COOC_2H_5$ (VI)

A possible scheme for the origin of the products formed from acetylene and diethyl carbonate follows:

$$Na_2C_2 + 2(C_2H_5O)_2CO \rightleftharpoons \underset{\text{VII}}{C_2H_5OOCC{\equiv}CCOOC_2H_5} + 2NaOC_2H_5$$

$$NaOC_2H_5 + HC{\equiv}CH \rightleftharpoons \underset{\text{VIII}}{C_2H_5OH} + NaC{\equiv}CH$$

$$Na_2C_2 + C_2H_2 \rightleftharpoons 2NaC{\equiv}CH$$

$$NaC{\equiv}CH + (C_2H_5O)_2CO \rightleftharpoons \underset{\text{IX}}{HC{\equiv}CCOOC_2H_5} + NaOC_2H_5$$

$$\text{VIII} + \text{IX} \xrightleftharpoons{\text{Michael condensation}} \text{I}$$

$$\text{I} + \text{VIII} \xrightleftharpoons{\text{Michael condensation}} \text{II}$$

$$\text{VII} + \text{VIII} \xrightleftharpoons{\text{Michael condensation}} \text{III}$$

$$\text{III} + \text{VIII} \xrightleftharpoons{\text{Michael condensation}} \text{IV}$$

3. Synthesis of acetylenic carbinols and related compounds

The sodium and lithium derivatives of acetylene and monosubstituted acetylenes have been added to a large number of aldehydes (179, 276, 409, 767, 893) and the following types of ketones: aliphatic and aromatic (29, 43, 92, 93, 179, 242, 405, 406, 409, 477, 478, 521, 560, 561, 609, 639, 782, 840); carbocyclic (53, 149, 252, 398, 402, 476, 610); heterocyclic (21, 348); α,β-unsaturated (248, 401, 465, 468, 674); miscellaneous (202, 450, 522, 524, 662).

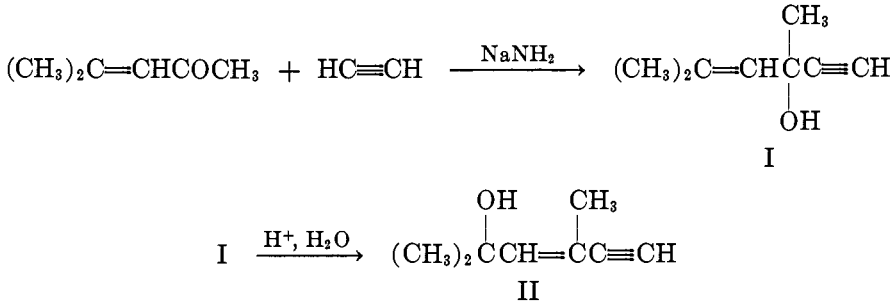
Because of the limitations of space only a few specific examples will be given. Sodium acetylide has been added to pentanal (893) to give 1-heptyn-3-ol (37 per cent yield) and sodio-1-hexyne has been added to methyl *n*-propyl ketone (179) to give 4-methyl-5-decyn-4-ol (65 per cent yield). Sodium acetylide has been condensed with 2-methylcyclohexanone (610) to give 1-ethynyl-2-methylcyclohexanol (67 per cent yield) and with 2-acetylthiophene (348) to give 3-(2-thienyl)-1-butyn-3-ol (30 per cent yield). The following equation illustrates these syntheses:

$$HC{\equiv}CC_4H_9\text{-}n + CH_3COC_3H_7\text{-}n \xrightarrow[(2)\ H_2O]{(1)\ NaNH_2,\ NH_3} n\text{-}C_3H_7C(OH)CH_3C{\equiv}CC_4H_9\text{-}n$$

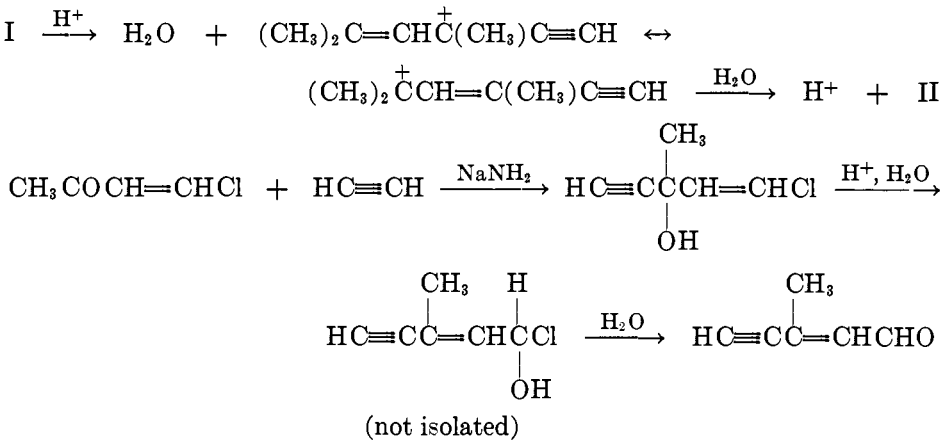
(65%) (179)

Mesityl oxide and related α,β-unsaturated ketones (248) have been treated with sodium acetylide to give acetylenic carbinols which, by reaction with

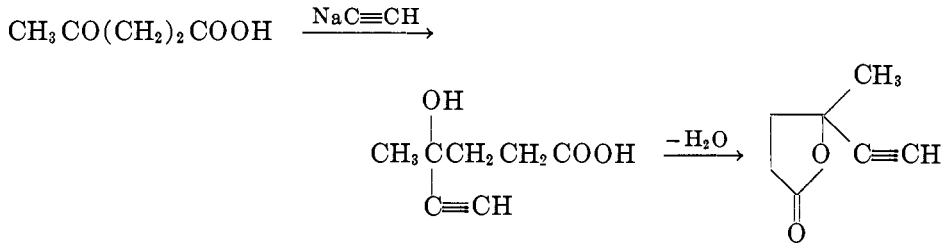
aqueous acid, may be isomerized to carbinols containing conjugated multiple bonds.



The rearrangement of I to II is believed to involve the conversion of I to a carbonium ion, followed by bond isomerization. A somewhat similar reaction (465) occurs when methyl β-chlorovinyl ketone is treated with sodium acetylide to give 3-methyl-2-penten-4-ynal.



Kreimeier (522) has reported that the reaction of γ-keto acids with sodium acetylide in liquid ammonia solution produces γ-ethynyl-γ-valerolactones.



4. Synthesis of di- and polyacetylenes

Under appropriate reaction conditions (759) sodium acetylide has been used as a starting material for the synthesis of diacetylenes. Thus, diacetylene (I) has been prepared in 5 per cent yield by bubbling oxygen through a liquid

ammonia solution of sodium acetylide and in 35 per cent yield by the oxidation of sodium acetylide with potassium permanganate. The alkylation of sodium acetylide with methylene chloride or propargyl bromide gives methyldiacetylene (II) (8–24 per cent yield), while its reaction with ethylene dibromide gives a 6–10 per cent yield of dipropargyl (III), which has been treated (812) with sodium amide and ethyl iodide to give a 61 per cent yield of 1,5-octadiyne.

$$NaC{\equiv}CH \xrightarrow[\text{or } KMnO_4]{NH_3 \text{ and } O_2} HC{\equiv}CC{\equiv}CH$$

I

Diacetylene

$$3NaC{\equiv}CH + ClCH_2Cl \rightarrow HC{\equiv}CCH_2C{\equiv}CNa + 2NaCl + HC{\equiv}CH$$

II

$$2NaC{\equiv}CH + BrCH_2C{\equiv}CH \rightarrow II + NaBr + HC{\equiv}CH$$

$$2NaC{\equiv}CH + BrCH_2CH_2Br \rightarrow HC{\equiv}CCH_2CH_2C{\equiv}CH + 2NaBr$$

III

Dipropargyl

Reaction of diacetylene with vinyl bromide and sodium amide appears to give some vinyldiacetylene (409). The alkylation of diacetylenes has been used (714, 715, 716) as a route to the synthesis of geometrical isomers of the insecticides pellitorine and herculin. While it is known that both double bonds have the *cis* configuration in the synthetic materials, the configurations of the double bonds in the naturally occurring materials have apparently not yet been established. The synthesis of the pellitorine isomer follows. In the synthetic geometrical isomer of herculin four methylene groups separate the olefinic linkages of V.

$$HC{\equiv}C(CH_2)_2C{\equiv}CH \xrightarrow[(3)\ C_2H_5MgBr,\ (4)\ CO_2]{(1)\ NaNH_2,\ (2)\ n\text{-}C_3H_7I} n\text{-}C_3H_7C{\equiv}C(CH_2)_2C{\equiv}CCOOH$$

IV

$$IV \xrightarrow[(3)\ H_2,\ Pd\text{-}CaCO_3]{(1)\ COCl_2,\ (2)\ i\text{-}C_4H_9NH_2} n\text{-}C_3H_7CH{=}CH(CH_2)_2CH{=}CHCONHC_4H_9\text{-}i$$

V

The syntheses of dialkyl- and diarylpolyacetylenes have been investigated (466). The preparation of dimethylpentaacetylene (VII) is typical of the methods employed. In actual practice the monosodium diacetylide, which is required

$$CH_3CHO + Na(C{\equiv}C)_2H \rightarrow CH_3CH(OH)(C{\equiv}C)_2H \xrightarrow{Cu_2Cl_2,\ O_2}$$

$$CH_3\overset{H}{\underset{OH}{C}}(C{\equiv}C)_4\overset{H}{\underset{OH}{C}}CH_3 \xrightarrow[(2)\ NaNH_2]{(1)\ SOCl_2} CH_3(C{\equiv}C)_5CH_3$$

VI VII

for the reaction with acetaldehyde, is prepared *in situ* by the reaction of 1,4-dichloro-2-butyne with sodium amide. The conversion of VI to VII occurs via the intermediate formation of the corresponding tetraacetylene dihalide, which is dehydrohalogenated by the sodium amide.

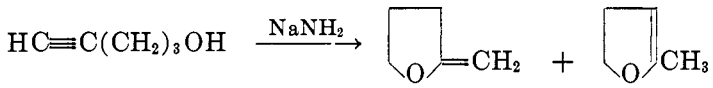
5. Other reactions of acetylene

Truchet (847) has studied the preparation of halogenated acetylenes. Here, R may be an aliphatic or aromatic radical, Ar is a phenyl or *p*-tolyl radical, and X is chlorine, bromine, or iodine. When R is aromatic, yields as high as 70 per cent

$$RC{\equiv}CH \xrightarrow[(2)\ ArSO_2X]{(1)\ NaNH_2} RC{\equiv}CX + ArSO_2Na$$

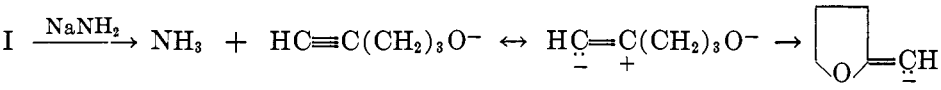
have been obtained, while 25 to 50 per cent yields were obtained when R is an aliphatic group. 1-Chloro- and 1-iodo-1-heptynes have been prepared (594) by treating the potassium derivatives of 1-heptyne with chlorine or iodine at −70°C.

Distillation of 1-pentyn-5-ol (I) over sodium amide (689) gives a mixture of 2-methylenetetrahydrofuran (II) and 2-methyl-4,5-dihydrofuran (III).



I II III

The sodium amide probably reacts with the hydroxyl hydrogen atom of I to give a resonating anion which undergoes cyclization to IV, which in turn reacts with a proton donor such as ammonia or some of I to give the mixture of II and III.



IV

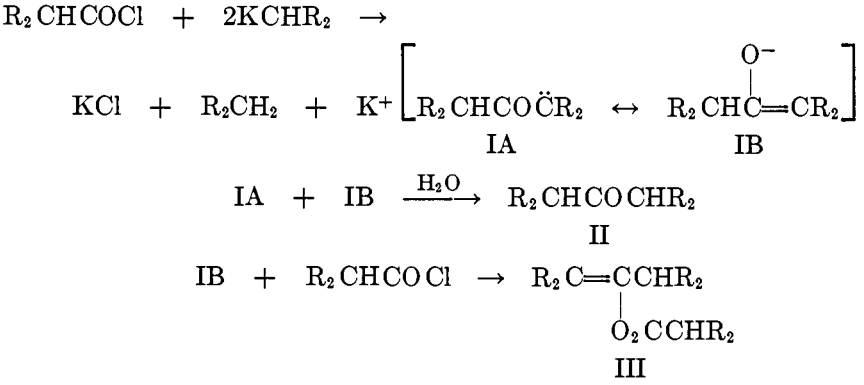
$$IV \xrightarrow{\text{proton donor}} II \rightleftharpoons III$$

C. AROMATIC HYDROCARBONS

Potassium diphenylmethide, prepared by the reaction of diphenylmethane with potassium amide in liquid ammonia (768), is arylated by chlorobenzene to give a mixture of triphenylmethane (11 per cent yield) and tetraphenylmethane (18 per cent yield). Yost and Hauser (900) have also found that it may be carbonated to give diphenylacetic acid (90 per cent yield), carbethoxylated with diethyl carbonate to give ethyl diphenylacetate (52 per cent yield), and benzoylated with methyl benzoate to give phenyl benzhydryl ketone (55 per cent yield).

sym-Tetraphenylacetone (II) is obtained by the interaction of equivalents of potassium diphenylmethide and diphenylacetyl chloride (31 per cent yield) or diphenylketene (15 per cent yield) (254). However, it has been found that

the yield of II may be increased to 72 per cent by using two equivalents of potassium diphenylmethide per equivalent of diphenylacetyl chloride. In this reaction some III, the enol diphenylacetate of II, is also formed (473).



R = C_6H_5.

Reaction of triphenylmethane with potassium amide gives potassium triphenylmethide (551), which has been carbonated to triphenylacetic acid (91 per cent yield). Potassium triphenylmethide has been arylated by chlorobenzene in liquid ammonia (768) to give tetraphenylmethane (45 per cent yield). In this connection it is interesting to note that lithium triphenylmethide, prepared from lithium diethylamide and triphenylmethane, is not arylated by bromobenzene in an ether medium (427).

Fluorene has also been metalated by reaction with potassium amide in liquid ammonia to give 9-potassiofluorene, which has been arylated with bromobenzene to give a mixture of 9-phenylfluorene (35 per cent yield) and 9,9-diphenylfluorene (16 per cent yield) (768).

The sodium derivative of fluorene has been alkylated with a large number of alkylating agents (278, 356). Thus, its reaction with 2-diethylaminoethyl chloride gives 9-(2-diethylaminoethyl)fluorene (278); with allyl chloride, 9-allylfluorene was obtained (356). The sodium derivatives of 1,2,3,4-tetrahydrofluorene (203, 206, 418) and 9,10-dihydroanthracene (322, 325) have been alkylated with a variety of halides.

It has been found that hydrogen–deuterium exchange between aromatic hydrocarbons and deuteroammonia (ND_3) is catalyzed by potassium amide (776). Thus, if naphthalene is dissolved in deuteroammonia which is 0.2 molar with respect to potassium amide, all of its hydrogen atoms are exchanged with deuterium in 10 min. at 25°C., while in the absence of potassium amide, no exchange occurs in 100 hr. at 120°C.

IV. Halogen Compounds

A. Alkyl and aralkyl halides

The reactions of alkyl halides with alkali amides in liquid ammonia have been studied (785, 787). The products isolated, which may consist of a mixture of

primary amines, secondary amines, and olefins, were found to depend on the structure of the alkyl halide and the halogen.

The dehydrohalogenation of alkyl and aralkyl halides has been investigated (390, 412). Thus, while the reaction of potassium amide with 1-bromo-2-phenylpropane in liquid ammonia solution gives "practically entirely" (390) 2-phenylpropene, its reaction with 1-bromo-2-phenylbutane gives a mixture of 2-phenyl-1-butene (I) and 2-phenyl-2-butene (II), with considerably more of I than II being formed. It is quite probable that II is formed from I by a prototropic shift, since reaction of a mixture of I and II with excess potassium amide gave only II.

$$CH_3CH_2CH(C_6H_5)CH_2Br \xrightarrow{KNH_2,\ NH_3}$$

1-Bromo-2-phenylbutane

$$CH_3CH_2\overset{\displaystyle C_6H_5}{\overset{|}{C}}{=}CH_2 \quad \text{and} \quad CH_3\overset{\displaystyle C_6H_5}{\overset{|}{C}}{=}CHCH_3$$

I II

When neophyl chloride is treated with sodium amide at 110–115°C., 1-methyl-1-phenylcyclopropane (III) (10.7 per cent yield), β,β-dimethylstyrene (IV) (18 per cent yield), and 70.7 per cent of recovered starting halide are isolated (879). A possible course for this reaction involves the removal of chloride ion from the neophyl chloride by the potentially available sodium ion of sodium

$$C_6H_5C(CH_3)_2CH_2Cl \xrightarrow[110\text{–}115°C.]{NaNH_2} C_6H_5\overset{\displaystyle CH_3}{\overset{|}{C}}\!\!<\!\!\begin{matrix}CH_2\\CH_2\end{matrix} + C_6H_5CH{=}C(CH_3)_2$$

Neophyl chloride III IV

amide to give the carbonium ion V, which may stabilize itself by ring formation or by rearrangement followed by olefin formation.

$$C_6H_5\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2Cl + NaNH_2 \rightarrow NaCl + NH_2^- + C_6H_5\overset{\displaystyle CH_3}{\overset{|}{C}}\overset{+}{C}H_2$$

V

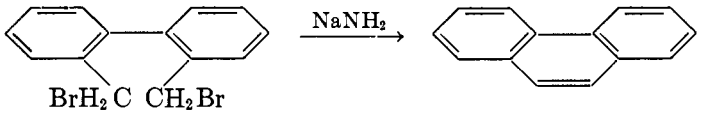
$$NH_2^- + V \rightarrow III + NH_3$$

$$V \xrightarrow{:C_6H_5\ \text{shift}} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}\overset{+}{C}HCH_2C_6H_5$$

VI

$$NH_2^- + VI \rightarrow IV + NH_3$$

2,2′-Dibromomethyldiphenyl is converted to phenanthrene in 80 per cent yield when it is treated with sodium amide in liquid ammonia (482).



B. UNSATURATED MONOHALIDES

The following general equation, where R is an alkyl or aryl radical and X is a halogen atom, indicates the method employed by a number of workers (95, 96, 256, 299, 352, 360, 449, 701, 710, 756, 859) for the preparation of acetylenes by the dehydrohalogenation of olefinic halides by sodium amide.

$$RCX{=}CH_2 \text{ (or } RCH{=}CHX) + 2NaNH_2 \rightarrow RC{\equiv}CNa + NaX + 2NH_3$$

$$RC{\equiv}CNa \xrightarrow{H^+,\ H_2O} RC{\equiv}CH$$

Thus, 2,4,6-trimethyl-α-chlorostyrene has been converted to mesitylacetylene in 71 per cent yield (859) and 1-bromo-3-methyl-1-butene has been dehydrohalogenated (256) to isopropylacetylene (34 per cent yield). 3-Bromo-2-pentenoic acid (756) is apparently not dehydrohalogenated when treated with sodium amide in aromatic solvents at 150°C.

Several 3-alkylamino-2-bromopropenes have been dehydrohalogenated to the corresponding *N*-allylidenealkylamines, probably via the isomeric allenes (689).

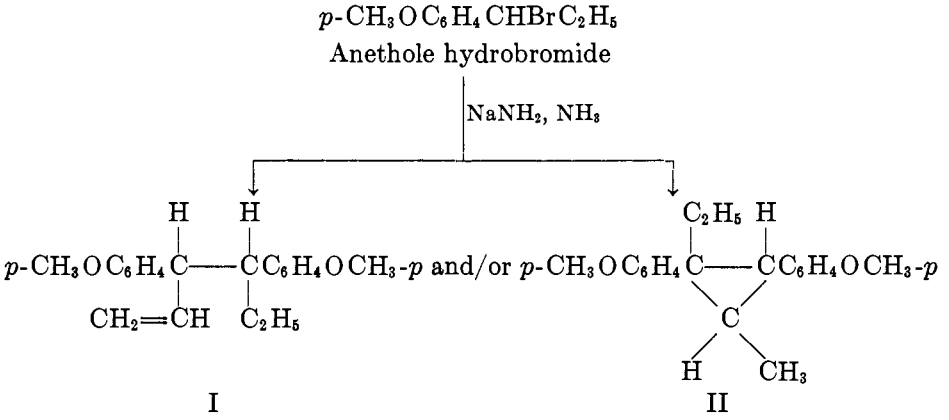
$$C_2H_5NHCH_2CBr{=}CH_2 \xrightarrow{NaNH_2} C_2H_5NHCH{=}C{=}CH_2 \rightarrow C_2H_5N{=}CHCH{=}CH_2 \quad (55\%)$$

2-Bromo-3-diethylaminopropene has been converted to the sodium derivative of 3-diethylaminopropyne, which has been alkylated with several alkyl halides in good yields (682).

$$(C_2H_5)_2NCH_2CBr{=}CH_2 \xrightarrow{NaNH_2} (C_2H_5)_2NCH_2C{\equiv}CNa \xrightarrow{RX} (C_2H_5)_2NCH_2C{\equiv}CR$$

Kharasch and coworkers (496, 497, 499–502) have studied carefully and in great detail the reaction of sodium amide with a number of saturated and unsaturated halides. They have done much to elucidate the mechanism by which allyl chloride and β-methylallyl chloride condense in liquid ammonia solution in the presence of sodium amide to produce the polyenes hexatriene (502) and 2,5-dimethylhexatriene (501), respectively. In connection with this study,

diethylstilbestrol has been prepared in an overall yield of 22 per cent starting with anethole hydrobromide (499).



I — 3,4-Di(*p*-methoxyphenyl)-1-hexene

II — 1-Methyl-2,3-di(*p*-methoxyphenyl)-3-ethylcyclopropane

$$\text{I and/or II} \xrightarrow[225°\text{C., 18 hr.}]{\text{KOH in ethylene glycol,}} p\text{-HOC}_6\text{H}_4\text{C}(\text{C}_2\text{H}_5)=\text{C}(\text{C}_2\text{H}_5)\text{C}_6\text{H}_4\text{OH-}p$$

Diethylstilbestrol

C. POLYHALIDES

Many vicinal dihalides have been dehydrohalogenated by sodium amide or sodioaniline (82) to give acetylenes in fair to good yields (117, 178, 237–239, 257, 494, 495, 536, 545–550, 627, 702). Thus, styrene dibromide (178) gives phenylacetylene (45–52 per cent); 3,4-dibromo-2-methylbutane (257) yields isopropylacetylene (28 per cent); 9,10-dibromostearic acid (495) is converted into stearolic acid (58–68 per cent); and 10,11-dibromoundecanoic acid (494) is dehydrohalogenated to 10-undecynoic acid (38–49 per cent).

$$\text{BrCH}_2\text{CHBr}(\text{CH}_2)_8\text{COOH} \xrightarrow[(2)\ \text{HCl}]{(1)\ 3\text{NaNH}_2} \underset{(38\text{–}49\%)}{\text{HC}\equiv\text{C}(\text{CH}_2)_8\text{COOH}} \underset{(494)}{} + 2\text{NaBr} + \text{NaCl} + 3\text{NH}_3$$

Paulson and MacGregor (691) have found that the products obtained when α,β-dibromocinnamic acid (I) is treated with sodium amide in liquid ammonia depend on the molecular proportions of the reactants used. The interaction of equivalents of reactants results in an 83 per cent recovery of I. When one equivalent of I is treated with three equivalents of sodium amide, *trans*-cinnamic acid (82 per cent yield) is obtained, while the interaction of one equivalent of I with two equivalents of sodium amide gives a mixture of trans-α-bromocinnamic acid (15 per cent yield) and *cis*-β-bromocinnamic acid (27 per cent yield).

The *gem*-dihalide 2,2-dichlorobutane has been dehydrochlorinated (832) to

2-butyne (40 per cent yield) and 1,1-dichloro-2,2-dimethylcyclohexane has been converted to 1-chloro-6,6-dimethylcyclohexene (131).

1-Phenyl-1,2,3,4-tetrabromobutane has been converted to phenyldiacetylene (633, 635).

$$C_6H_5(CHBr)_3CH_2Br + 5NaNH_2 \xrightarrow{NH_3} \underset{I}{C_6H_5(C{\equiv}C)_2Na} + 4NaBr + 5NH_3$$

$$I \xrightarrow{\text{hydrolysis}} C_6H_5(C{\equiv}C)_2H$$

D. UNSATURATED POLYHALIDES

There has been considerable activity in the area of synthesizing polyacetylenes and their derivatives by the dehydrohalogenation of acetylenic dihalides with sodium amide (26–28, 120, 121, 219, 525, 581, 634). These syntheses may be represented by the following general equation, where X is a chlorine or bromine atom and n is 1 or >1. Compound II may be hydrolyzed to give the polyacetylene, $H(C{\equiv}C)_{n+1}H$, or it may be treated *in situ* with other reagents such as alkyl halides, aldehydes, and ketones.

$$\underset{I}{XCH_2(C{\equiv}C)_nCH_2X} + 4NaNH_2 \xrightarrow{NH_3} \underset{II}{Na(C{\equiv}C)_{n+1}Na} + 2NaX + 4NH_3$$

Thus, 1,4-dichloro-2-butyne (27, 28) has been converted to the disodium derivative of diacetylene (II, n = 1), which has been treated with a number of alkyl halides to give, depending on reaction conditions, mono- or dialkylated derivatives of diacetylene. II (n = 1) has also been condensed with a number of carbonyl compounds to give the corresponding diacetylenic alcohols and/or diacetylenic glycols. This reaction has been extended to 1,6-dichloro-2,4-hexadiyne (I, n = 2) (26) and 1,8-dichloro-2,4,6-octatriyne (I, n = 3) (219) with similar results.

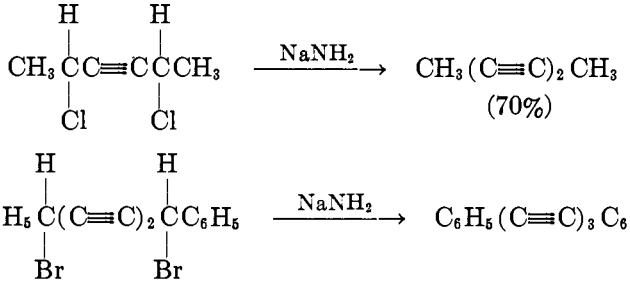
$$Na(C{\equiv}C)_2Na \xrightarrow[(2)\ H_2O]{(1)\ CH_3I} CH_3(C{\equiv}C)_2H \quad \text{and/or} \quad CH_3(C{\equiv}C)_2CH_3$$

$$Na(C{\equiv}C)_2Na \xrightarrow[(2)\ H_2O]{(1)\ CH_3COCH_3}$$

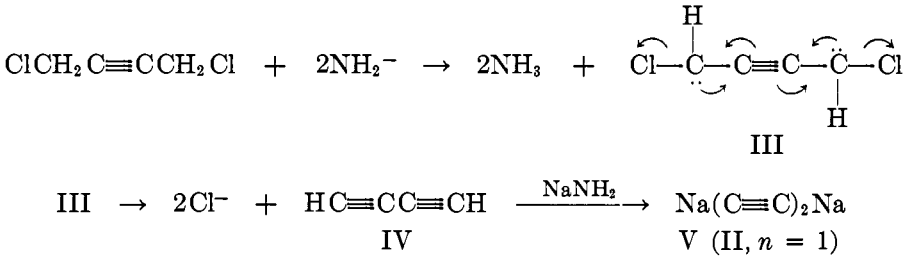
$$(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}(C{\equiv}C)_2H \quad \text{and/or} \quad (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}(C{\equiv}C)_2\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)_2$$

This reaction has also been used successfully where one of the hydrogen atoms of each of the methylene groups of I has been replaced by an alkyl or aryl group. Thus, 2,5-dichloro-3-hexyne (219) has been converted to 2,4-hexadiyne (70

per cent) and 1,6-dibromo-1,6-diphenyl-2,4-hexadiyne has been dehydrohalogenated (581, 634) to diphenyltriacetylene.



A possible electronic interpretation for the conversion of compounds of type I to those of type II follows, using 1,4-dichloro-2-butyne as an example.



III

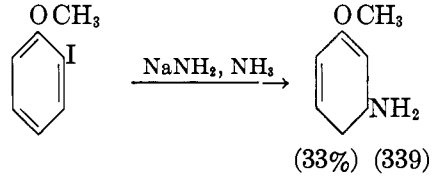
The butyne is probably first converted to the dianion III, which by a shift of electron pairs and the loss of two chloride ions gives IV. Compound IV then undergoes an acid–base reaction with sodium amide to form V.

E. AROMATIC HALIDES

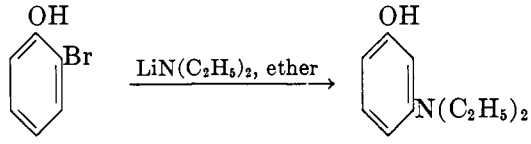
Bergstrom and Horning (86) have found that the reaction of potassium amide in liquid ammonia with 9-bromophenanthrene gives 9-aminophenanthrene, while its reaction with *p*-tolyl bromide gives a mixture of *p*-tolylamine, di-*p*-tolylamine, and tri-*p*-tolylamine.

Urner and Bergstrom (851) have treated 1-chloro-, 1-bromo-, and 1-iodonaphthalenes with potassium amide in liquid ammonia and from each of these reactions traces of the normal product 1-naphthylamine (2–3 per cent), and large amounts (43–53 per cent) of the rearranged product, 2-naphthylamine, were obtained. However, under the same conditions 1-fluoronaphthalene gave only 1-naphthylamine and all the 2-naphthyl halides gave 2-naphthylamine as the main reaction product. When 1-chloro-, 1-bromo-, and 1-fluoronaphthalenes are treated with lithium diethylamide (340), a mixture of naphthalene, 1-halonaphthalene, and 2-diethylaminonaphthalene (rearranged product) was obtained and none of the expected 1-diethylaminonaphthalene was isolated. Massie (582) has treated 1-bromonaphthalene with lithium didodecylamide and obtained 2-didodecylaminonaphthalene (42 per cent).

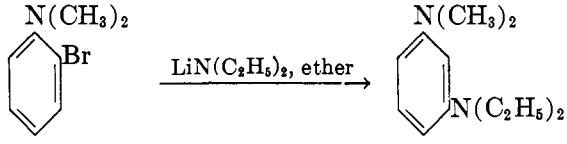
A number of *o*- and *p*-halogenated aryl alkyl ethers (63, 339, 341, 342), *o*-halogenated aryl alkyl sulfides (344, 574), *o*-halophenols (341), and *o*-halo-*N*,*N*-dialkylanilines (343) have been treated with lithium amide, sodium amide, potassium amide, lithium diethylamide, and *N*-lithiopiperidine to give products in which the halogen atom has been eliminated and an amino or substituted amino group has been introduced into the ring in a position meta to the ether, thioether, phenolic, or *N*,*N*-dialkylamino function. When either *o*- or *m*-chlorobenzotrifluoride is treated with sodium amide in liquid ammonia, *m*-aminobenzotrifluoride is obtained (64).



(33%) (339)

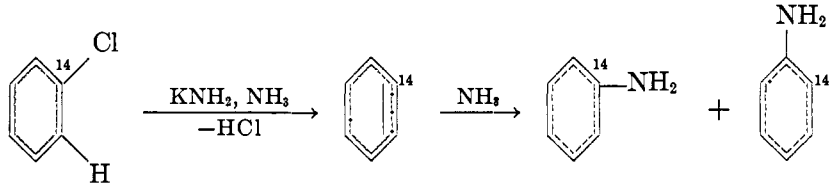


(341)



(343)

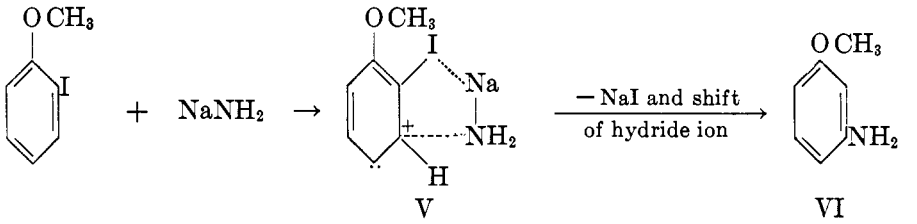
Roberts and coworkers (732) have proposed that these reactions may proceed by an elimination–addition mechanism which involves the transitory existence of an electrically neutral "benzyne" intermediate (II). Support for this mechanism was obtained when it was found that treatment of chlorobenzene-1-C^{14} (I) with potassium amide in liquid ammonia gave essentially equal amounts of aniline-1-C^{14} (III) and aniline-2-C^{14} (IV).



I II III IV

An alternative explanation for the formation of the rearranged products is to assume the formation of the quasi-five-membered ring, V, shown below for the case of *o*-iodoanisole. The loss of sodium iodide, the shift of a hydride ion,

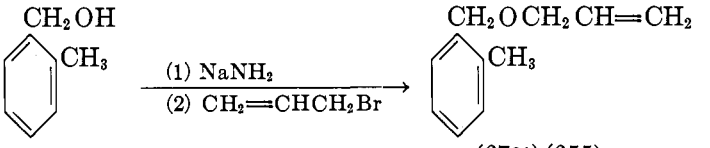
and the reëstablishment of the aromatic ring then give the rearranged product (VI). The presence of an ether or similar electron-releasing function ortho or



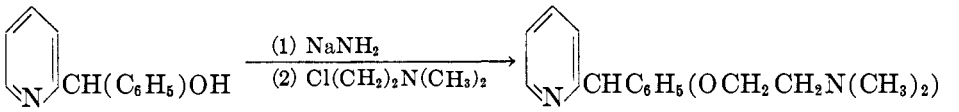
para to the carbon atom carrying the halogen increases the electron density at this carbon atom and facilitates the removal of the halogen as halide ion.

V. Alcohols, Mercaptans, Phenols, and Ethers

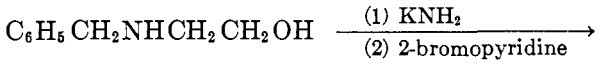
A large number of carbinols containing aliphatic, carbocyclic, aromatic, and heterocyclic radicals have been treated with alkali amides to give metallic derivatives which have been etherified by reaction with a variety of reagents such as alkyl halides (511, 655, 685, 687), heterocyclic halides (820, 838), dialkyl sulfates (625, 810), and dialkylaminoalkyl halides (305, 306, 308, 310, 328, 329, 333, 334, 575, 579, 703, 705–708, 815, 820, 821, 853, 895). The following examples are typical.

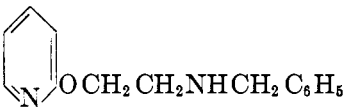


(67%) (655)

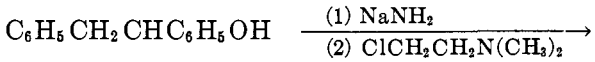


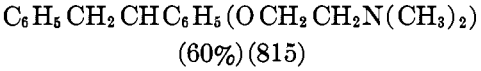
(82%) (821)





(35%) (838)

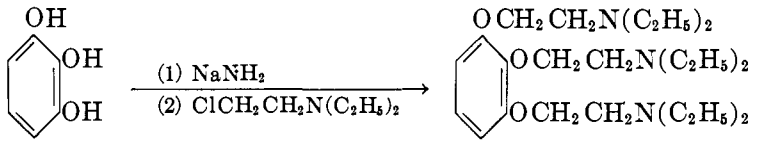




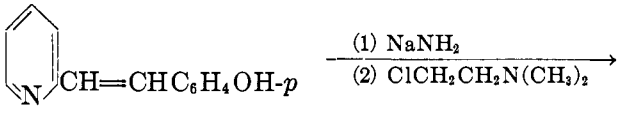
(60%) (815)

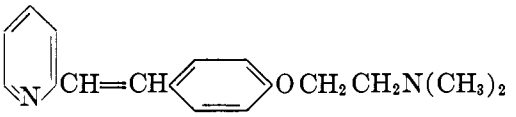
Mercaptans have also been alkylated (415, 416, 706). Thus, benzhydryl mercaptan has been condensed with 2-(1-piperidyl)ethyl chloride to give benzhydryl 2-(1-piperidyl)ethyl sulfide (706).

The alkylation of phenols has also been studied (290, 615, 680, 681), as shown in the following examples. Some of the ethers derived from the alkylation of phenols and alcohols with 2-dialkylaminoethyl halides have had some application as antihistaminic agents.



(290)





(88%) (680, 681)

Hauser and Breslow (379) have found that benzylphenylcarbinol is not dehydrated by sodium amide in ethyl ether at room temperature.

The use of sodium amide as a reagent to determine the active hydrogen content of alcohols has been studied (678, 679). The method, which involves the titration of the ammonia liberated when the alcohols are treated with sodium amide, is not too satisfactory, since ammonia in excess of the theoretical amount is usually produced, probably owing to the ammonia occluded in the sodium amide.

Hauser and Kantor (385) have studied and proposed a mechanism for the elimination and isomerization reactions which occur when certain benzyl ethers are treated with potassium amide in liquid ammonia. Thus, the anion of dibenzyl ether, formed by reaction with potassium amide, undergoes both β-elimination to form benzamide and toluene and isomerization to give benzylphenylcarbinol. However, dibenzhydryl ether, when treated similarly, undergoes only β-elimination, forming benzophenone, benzamide, and diphenylmethane.

The reactions of the cyclic ethers epichlorohydrin and 3-phenylpropylene oxide have been discussed in Section III,B,1 of this review. Cyclohexene oxide has been cleaved by potassium amide in liquid ammonia to give *dl-trans*-2-aminocyclohexanol (591).

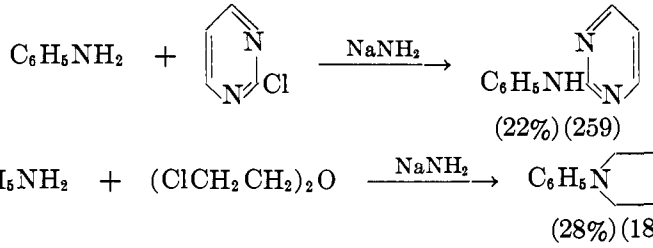
Sodium amide is ineffective in cleaving methyl and ethyl ethers of alicyclic alcohols without destroying the configuration of the alicyclic residues (441).

VI. Amines

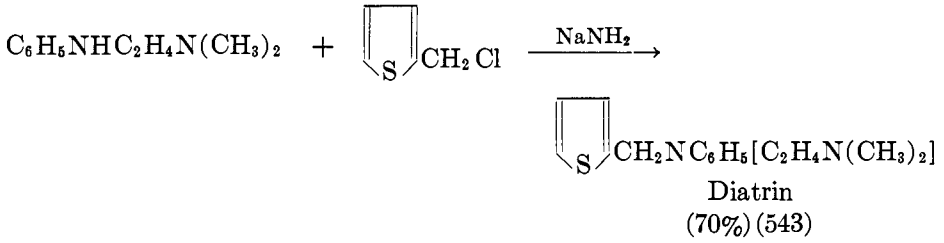
A. Alkylation and Arylation Reactions

A number of heterocyclic amines, which will be discussed in later sections of this review, and a variety of aromatic amines (97, 114, 148, 155, 168, 180, 187, 188, 191, 204, 220, 259, 278, 280, 447, 479, 492, 507, 543, 726, 727, 865) have been

treated with many alkyl and heterocyclic halides to give either secondary or tertiary amines depending on the structures of the amines and the halides.



A large number of tertiary amines containing 2-dialkylaminoethyl groups have been prepared and evaluated as antihistaminic agents. The synthesis of one of these compounds (Diatrin) follows:



Phenylhydrazine has been alkylated by reaction with sodium amide and alkyl halides in a liquid ammonia (36), ether (354), or benzene (354) medium.

$$C_6H_5NHNH_2 \xrightarrow[(2)\ RX]{(1)\ NaNH_2} C_6H_5NRNH_2$$

The following *N*-alkyl-*N*-phenylhydrazines have been prepared: ethyl (88 per cent yield), *n*-propyl (94 per cent yield), and benzyl (73 per cent yield) (36).

Benzaldehyde hydrazone has been alkylated with ethyl iodide to give benzaldehyde ethylhydrazone (770).

$$C_6H_5CH{=}NNH_2 \xrightarrow[(2)\ C_2H_5I]{(1)\ NaNH_2} C_6H_5CH{=}NNHC_2H_5$$

A number of dialkylarylamines (340, 427) have been prepared by treating lithium dialkylamides with aryl halides in ether or benzene solution. It has also been possible to arylate cyclohexylamine with bromobenzene in the presence

$$C_6H_5Cl + LiN(C_2H_5)_2 \rightarrow LiCl + \underset{(56\%)\ (427)}{C_6H_5N(C_2H_5)_2}$$

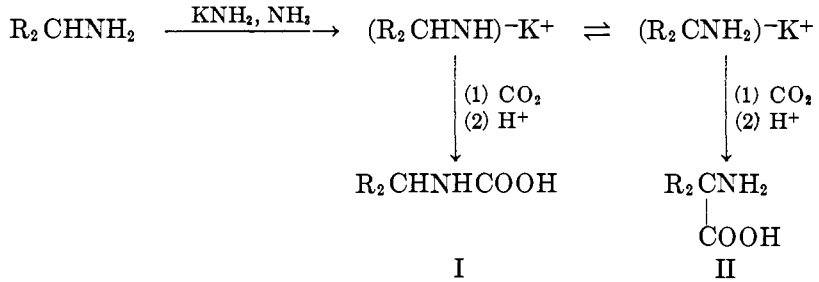
of potassium amide in liquid ammonia to give a mixture of cyclohexylaniline and cyclohexyldiphenylamine (768).

B. REACTIONS WITH ACYLATING AGENTS, CARBON DIOXIDE, AND CARBON DISULFIDE

The sodium derivatives of amines have been acylated with esters (458) and acid chlorides (315). Thus, the reaction of aniline, sodium amide, and methyl

methacrylate gives methacrylylaniline (41 per cent), while the acylation of phenylhydrazine with this ester gives *N*-methacrylyl-*N'*-phenylhydrazine (22 per cent) (458). It would be of interest to determine why the alkylation of phenylhydrazine gives unsymmetrical (36) and its acylation gives symmetrical (458) disubstituted hydrazines.

It has been found (380) that the reaction mixture of benzhydrylamine and potassium amide in liquid ammonia consists of a mixture of anions, since its carbonation gives both benzhydrylcarbamic acid (I) and 2-amino-2,2-diphenylethanoic acid (II). However, if the carbon dioxide is replaced by diethyl carbonate, only the ethyl ester of I is obtained.

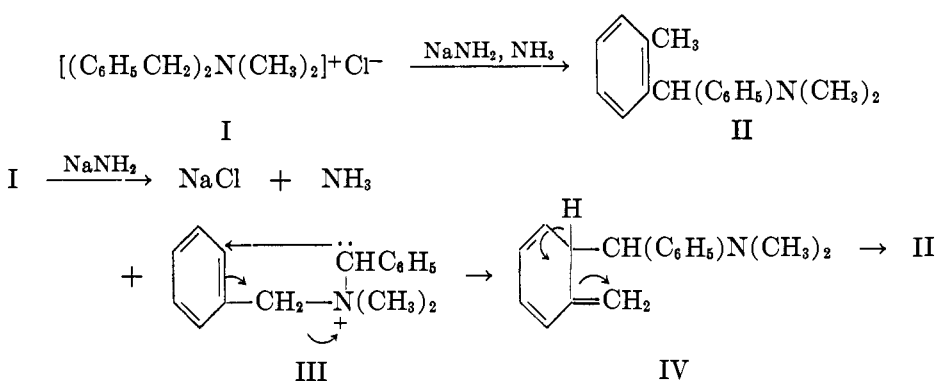


R = C_6H_5.

Lonsbury (564) has prepared sodium phenyl-β-naphthyldithiocarbamate by the reaction of phenyl-β-naphthylamine with sodium amide and carbon disulfide.

C. OTHER REACTIONS OF AMINES

Kantor and Hauser (474) have studied intensively the rearrangement of the benzyltrimethylammonium ion and related quaternary ammonium ions by sodium amide in liquid ammonia. Thus, dibenzyldimethylammonium chloride (I) is converted to *o*-(dimethylaminobenzyl)toluene (II) in 95 per cent yield. These workers have proposed the following course for these reactions: Compound I is converted to anion III, which undergoes intramolecular nucleophilic substitution to give IV, which in turn isomerizes to II.



While in the base-induced Stieglitz rearrangement (829) of tritylhaloamines the main reaction product is benzophenoneanil (V), Ayres and Hauser (38) have found that the reaction of *N*-trityl-*O*-benzylhydroxylamine with potassium amide gives less than 3 per cent of V. Instead, triphenylmethane (60–65 per cent) and benzaldoxime (25–37 per cent) are obtained.

Bergstrom (80) has observed that potassium amide reacts with potassium nitrate according to the following equation. He tried unsuccessfully to extend

$$3KNH_2 + 3KNO_3 \rightarrow 3KOH + 3KNO_2 + N_2 + NH_3$$

this to the preparation of triphenylamine by replacing the potassium amide by potassioaniline.

It has been found (85) that sodium diphenylamide and nitrobenzene react to give *p*-nitrotriphenylamine (45 per cent). The formation of this compound is easily explained, since the electrophilic nitro group activates the ortho and para positions of nitrobenzene to attack by a nucleophilic reagent such as the diphenylamine anion.

$$NaNH_2 + (C_6H_5)_2NH \rightarrow NH_3 + \underset{\text{VI}}{(C_6H_5)_2NNa}$$

$$\text{VI} + C_6H_5NO_2 \rightarrow NaH + (C_6H_5)_2NC_6H_4NO_2\text{-}p$$

VII. Aldehydes, Including Aldoximes and Anils

A number of crossed aldol condensations between citral and other aldehydes have been reported (55, 400). The formation of citrylideneacetaldehyde (I) is a typical example.

$$(CH_3)_2C{=}CHC_2H_4C(CH_3){=}CHCHO + CH_3CHO \xrightarrow{NaNH_2}$$

$$H_2O + \underset{\text{I}}{(CH_3)_2C{=}CHC_2H_4C(CH_3){=}CHCH{=}CHCHO}$$

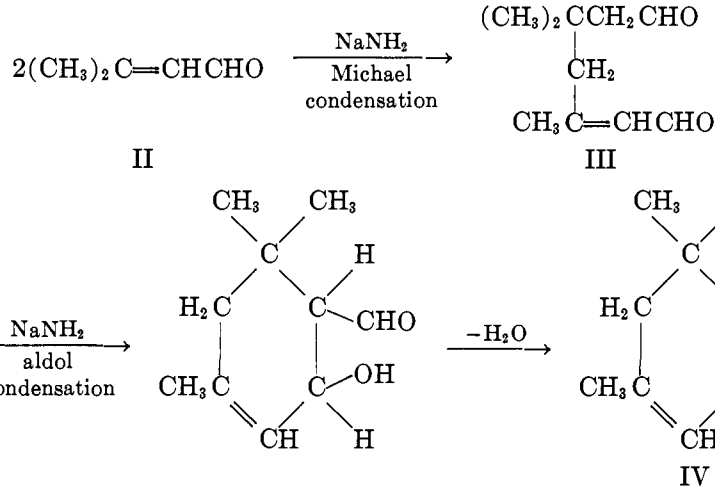
Stoll (830) has effected crossed aldol condensations between undecanal and acetaldehyde and obtained two isomeric hydroxyaldehydes.

$$\underset{\text{Undecanal}}{n\text{-}C_{10}H_{21}CHO} + \underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow{NaNH_2} CH_3(CH_2)_8\underset{\displaystyle CH_3\overset{|}{C}HOH}{\overset{|}{C}HCHO}$$

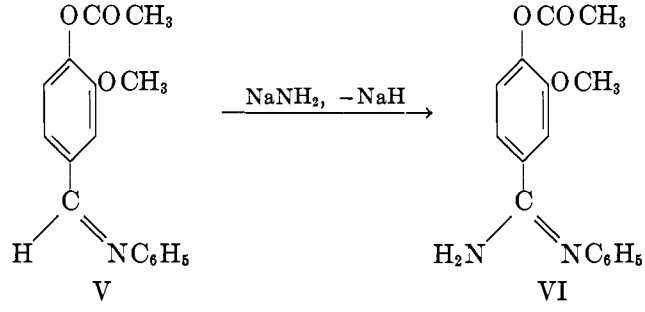
$$+ \quad n\text{-}C_{10}H_{21}CHOHCH_2CHO$$

The reaction of 3-methyl-2-butenal (II) with sodium amide gives 4,6,6-trimethyl-1,3-cyclohexadiene-1-carboxaldehyde (IV) (289). It appears that IV

arises from a Michael condensation between two molecules of II to give III, which then undergoes an intramolecular aldol condensation.



Challis and Clemo (190) have found that the reaction of *O*-acetylvanillin anil (V) with sodium amide gives *O*-acetyl-*N*-phenylvanillamidine (VI). The amidine appears to be formed by the addition of sodium amide across the azomethine linkage of V, followed by loss of sodium hydride.



The course of the reactions of potassium amide on several *syn-* and *anti-*aldoximes and their *O*-methyl and *O*-acetyl derivatives has been studied (384, 864). Thus, *syn-* and *anti-*4-methoxybenzaldoximes and their *O*-methyl ethers react quantitatively with potassium amide in liquid ammonia to give 4-methoxybenzonitrile.

VIII. Ketones

A. The Claisen Acylation of Ketones with Esters and Acid Chlorides

Hauser, Levine, and their coworkers (3, 374, 375, 378, 388, 391, 393, 552, 555, 556, 570, 628, 780, 800, 904) have studied extensively the use of sodium amide and lithium amide as condensing agents in the Claisen synthesis of β-diketones by the acylation of ketones with esters. Aliphatic, carbocyclic,

aromatic, and heterocyclic ketones have been acylated with aliphatic, aromatic, hydroaromatic, and heterocyclic esters. The synthesis of a typical β-diketone, di-*n*-butyrylmethane, follows.

$$CH_3COC_3H_7\text{-}n + n\text{-}C_3H_7COOC_2H_5 \xrightarrow{NaNH_2} C_2H_5OH + n\text{-}C_3H_7COCH_2COC_3H_7\text{-}n$$

The course of these acylations has been investigated (3, 904), and it was found that the yields of β-diketone (based on the ketone), which are less than 50 per cent when equivalents of reactants are used, are increased considerably when two equivalents of sodium amide are used for each equivalent of ester and ketone. Thus (3), employing the first set of conditions, di-*n*-butyrylmethane was prepared in 33 per cent yield, while under the second set of conditions a 68 per cent yield of β-diketone was obtained.

To account for the beneficial effect of the second equivalent of base, the following mechanism has been proposed for these acylations. When 1 mole of each of the reactants is used, the ketone is essentially completely converted to its anion

(1) $CH_3COR + NH_2^- \rightarrow (CH_2COR)^- + NH_3$

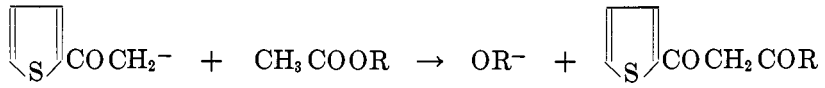
(2) $RCOOC_2H_5 + (CH_2COR)^- \rightarrow RCOCH_2COR + OC_2H_5^-$

(3) $RCOCH_2COR + (CH_2COR)^- \rightarrow (RCOCHCOR)^- + CH_3COR$
or
$RCOCH_2COR + NH_2^- \rightarrow (RCOCHCOR)^- + NH_3$

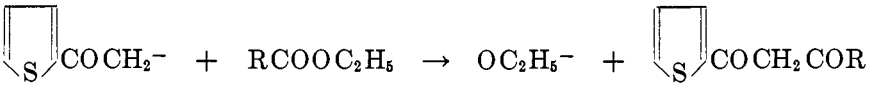
(step 1). Part of the ketone anion then condenses with the carbonyl group of the ester (step 2) to form the β-diketone, which then reacts rapidly in step 3 with some of the ketone anion to give the anion of the β-diketone. Theoretically, one-half of the starting ketone could be regenerated in this manner and the maximum yield of β-diketone would be 0.5 mole. However, when a second equivalent of amide ion is present, it effects the third step, since it is a stronger base than the ketone anion. Regeneration of the ketone from its anion is thus prevented and the maximum yield of product is 1 mole. It is also theoretically possible to obtain a mole of β-diketone from the interaction of 2 moles of amide ion, 2 moles of ketone, and 1 mole of ester.

In a formal way the second step of the Claisen condensation resembles the ammonolysis and alkaline hydrolysis of esters, in that all three of these reactions involve the attack of a nucleophilic reagent, i.e., the ketone anion, ammonia, or hydroxide ion, on the carbonyl carbon atom of an ester. As indicated in the following scheme, Sneed and Levine (800) have studied the reactions of a series of aliphatic and aromatic esters with the anion of 2-acetylthiophene, which was prepared by treating the ketone with sodium amide, and have found that the relative reactivity of the esters in the Claisen condensation parallels that

observed for these esters in their ammonolysis (353) and alkaline hydrolysis (371).



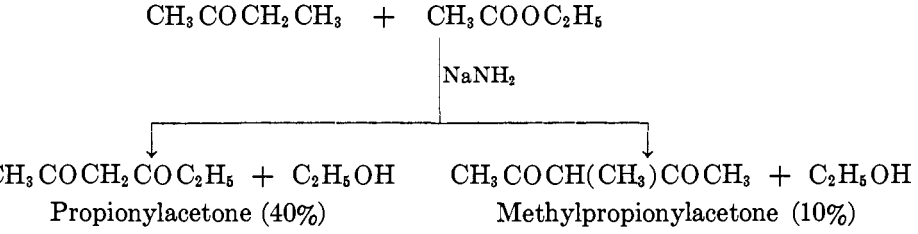
Reactivity of esters: R = C_6H_5 > CH_3 > C_2H_5 > i-C_3H_7 > t-C_4H_9



Reactivity of esters: R = CH_3 > C_2H_5 > i-C_3H_7 > t-C_4H_9

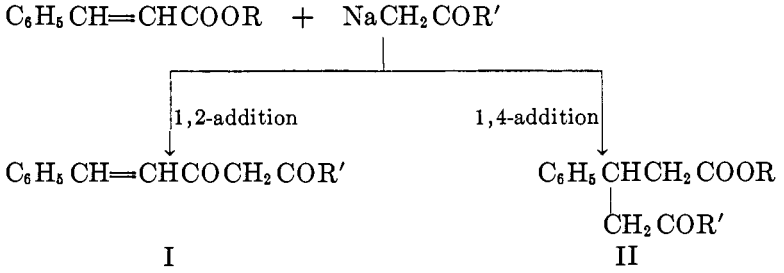
R = p-ClC_6H_4 > C_6H_5 > p-$CH_3OC_6H_4$

When a methyl ketone which has hydrogen atoms on only one of its two α-carbon atoms is acylated with an ester, only one β-diketone can be formed. However, if an unsymmetrical methyl alkyl ketone, such as methyl ethyl ketone, is acylated, isomeric β-diketones are often produced (3, 552), with reaction occurring predominantly at the α-methyl carbon atom.



Propionylacetone (40%) Methylpropionylacetone (10%)

When an ester of cinnamic acid is treated with the anion of a methyl ketone, reaction may occur by 1,2-addition (Claisen) of the anion to the ester to give a β-diketone or by 1,4-addition (Michael) to give a β-phenyl-γ-acylbutyric acid or its ester (393). Thus, the reaction of ethyl cinnamate with sodioacetophenone gives a 66 per cent yield of butyric acid (II: R = H, R′ = C_6H_5); the reaction of phenyl cinnamate with sodioacetophenone gives a mixture of 29 per cent I (R′ = C_6H_5) and 3 per cent II (R = H, R′ = C_6H_5), and the reaction of ethyl cinnamate with sodiopinacolone gives a 64 per cent yield of II (R = C_2H_5, R′ = t-C_4H_9). Because of the current interest in the use of



I II

β-diketones as chelating agents, the β-diketones, which have been synthesized by acylating ketones with esters and prepared since the publication of the last

review as well as those which were omitted from the earlier reviews (83, 84), are listed in table 1.

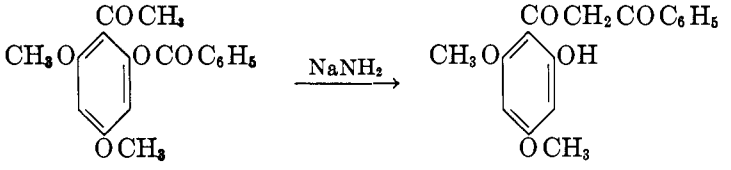
A few ketones have been acylated with acid chlorides, using sodium amide as the condensing agent (337, 393, 569, 586, 599, 891). Thus, the reaction of desoxybenzoin with propionyl chloride (393) gives a mixture of phenylpropionylbenzoylmethane (III) (minor product) and 1,2-diphenylvinyl propionate (IV) (major product). The reaction of sodioacetophenone with cinnamoyl chloride gives a 66 per cent yield of the diacylated ketone, dicinnamoylacetophenone (393).

$$RCH_2COR + C_2H_5COCl \xrightarrow{NaNH_2} \underset{\text{III}}{RCOCHRCOC_2H_5} + \underset{\text{IV}}{C_2H_5COOCR{=}CHR}$$

R = C_6H_5.

B. THE REARRANGEMENT OF *o*-AROYLOXYACETOPHENONES; THE VENKATARAMAN–BAKER TRANSFORMATION

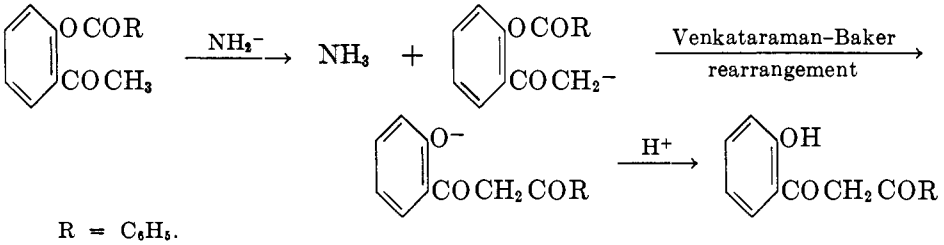
The rearrangement of *o*-aroyloxyacetophenones to *o*-hydroxydibenzoylmethanes by basic reagents such as sodium amide, which was reported in the last review (84), has been studied and extended by a number of workers (19, 23, 45–47, 267, 363, 426, 632, 748, 749). The following example (363) is typical.



2-Benzoyloxy-4,6-dimethoxyacetophenone

2-Hydroxy-4,6-dimethoxydibenzoylmethane (40%)

The mechanism of these rearrangements has been studied (250). These transformations, by which β-diketones are formed, may be regarded as intramolecular Claisen acylations. While in ordinary Claisen acylations the ketone and ester functions are not present in the same molecule, both of these functions are present in the ortho position to one another in compounds undergoing the Venkataraman–Baker transformation. In the following scheme, the course for the rearrangement of *o*-benzoyloxyacetophenone to *o*-hydroxydibenzoylmethane is indicated.



R = C_6H_5.

TABLE 1

β-Diketones by the acylation of ketones with esters

KETONE	ESTER	PRODUCT	YIELD*	REFERENCES
			per cent	
Acetone	Ethyl acetate	Acetylacetone	54, 50†	(3, 904)
	Ethyl propionate	Propionylacetone	60	(552)
	Ethyl isobutyrate	Isobutyrylacetone	42, 30	(3, 552)
	Ethyl laurate	Lauroylacetone	76	(552)
	Ethyl hexahydrobenzoate	Hexahydrobenzoylacetone	62	(552)
	Ethyl cinnamate	Cinnamoylacetone	6	(552)
	Phenyl cinnamate	Cinnamoylacetone	30	(393)
	Ethyl 2-furoate	Acetyl-2-furoylmethane	43	(375)
	Methyl acetoneglycerate	5,6-Dioxyisopropylidene-2,4-hexanedione	46	(631)
Methyl ethyl	Ethyl acetate	Propionylacetone	40	(552)
		Methylacetylacetone	10	
	Ethyl propionate	Dipropionylmethane	57, 51†	(3, 904)
		Methylpropionylacetone	13, 11†	
	Ethyl *n*-butyrate	Propionyl-*n*-butyrylmethane	60	(3)
	Ethyl benzoate	α-Propionylacetophenone	42	(552)
	Ethyl phenylacetate	Phenacylpropionylmethane	54	(552)
Methyl *n*-propyl	Ethyl acetate	*n*-Butyrylacetone	47	(552)
		Ethylacetylacetone	2	
	Ethyl propionate	Propionyl-*n*-butyrylmethane	70	(3)
		Ethylpropionylacetone	2	
	Ethyl *n*-butyrate	Di-*n*-butyrylmethane	78, 76†	(3, 904)
	Ethyl benzoate	α-*n*-Butyrylacetophenone	38	(552)
Methyl cyclopropyl	Ethyl acetate	1-Cyclopropyl-1,3-butanedione	75	(184)
	Ethyl benzoate	1-Cyclopropyl-3-phenyl-1,3-propanedione	68	(184)
	Phenyl benzoate	1-Cyclopropyl-3-phenyl-1,3-propanedione	40	(184)
	Ethyl phenylacetate	1-Cyclopropyl-4-phenyl-1,3-butanedione	24†	(797)
Methyl isopropyl	Ethyl *n*-butyrate	*n*-Butyrylisobutyrylmethane	59	(552)
Methyl *n*-butyl	Ethyl *n*-valerate	Di-*n*-valerylmethane	—	(260)
Methyl isobutyl	Ethyl acetate	Isovalerylacetone	59	(552)
	Ethyl *n*-butyrate	*n*-Butyrylisovalerylmethane	80	(3)
	Phenyl 2-ethylbutanoate	2-Methyl-7-ethyl-4,6-nonanedione	56	(570)
	Ethyl isovalerate	Diisovalerylmethane	76, 75, 75,† 69–79	(3, 552) (378, 904)
	Ethyl 2-furoate	Isovaleryl-2-furoylmethane	73	(375)

TABLE 1—*Continued*

KETONE	ESTER	PRODUCT	YIELD*	REFERENCES
			per cent	
Methyl *tert*-butyl..	Ethyl acetate	Pivaloylacetone	43	(3)
	Ethyl pivalate	Dipivaloylmethane	28	(3)
	Phenyl pivalate	Dipivaloylmethane	64	(570)
	Ethyl *n*-valerate	*n*-Valerylpivaloylmethane	52	(3)
	Methyl benzoate	Pivaloylbenzoylmethane	69	(556)
	Methyl nicotinate	Pivaloylnicotinoylmethane	60	(556)
Methyl *n*-amyl....	Ethyl acetate	Caproylacetone	61	(552)
		n-Butylacetylacetone	0.4	
	Ethyl caproate	Dicaproylmethane	73, 60, 65†	(3, 552, 904)
	Phenyl isobutyrate	2-Methyl-3,5-decanedione	50	(570)
	Phenyl 2-ethylbutanoate	3-Ethyl-4,6-undecanedione	51, 62†	(570)
	Phenyl 2-ethylhexanoate	5-Ethyl-6,8-tridecanedione	43	(570)
	Phenyl pivalate	2,2-Dimethyl-3,5-decanedione	46	(570)
	Ethyl 2-furoate	Caproyl-2-furoylmethane	73	(375)
unsym-Diethylacetone.....	Phenyl 2-ethylbutanoate	3,7-Diethyl-4,6-nonanedione	62	(570)
3,7,11,15-Tetramethyl-2-hexadecanone.....	Ethyl acetate	5,9,13,17-Tetramethyl-2,4-octadecanedione	58	(793)
1-Diethylamino-4-pentanone.....	Ethyl 2-phenyl-7-chlorocinchoninate	1-(7′-Chloro-2′-phenylquinoline-4′)-6-diethylamino-1,3-hexanedione	15	(780)
Cyclopentanone...	Methyl benzoate	α-Benzoyl-α'-cyclopentylidenecyclopentanone	21	(388)
1,2,2,3-Tetramethyl-1-acetylcyclopentane.....	Ethyl benzoate	1,2,2,3-Tetramethyl-1-benzoylacetylcyclopentane	Good	(741)
Cyclohexanone....	Ethyl acetate	2-Acetylcyclohexanone	35	(552)
	Ethyl propionate	2-Propionylcyclohexanone	4	(552)
	Ethyl *n*-butyrate	2-*n*-Butyrylcyclohexanone	6–12	(552)
	Methyl benzoate	2-Benzoylcyclohexanone	47	(388)
	Phenyl benzoate	2-Benzoylcyclohexanone	69	(388)
	Phenyl anisate	2-Anisoylcyclohexanone	46	(391)

TABLE 1—*Continued*

KETONE	ESTER	PRODUCT	YIELD*	REFERENCES
			per cent	
2,4-Dimethylcyclohexanone	Amyl formate	6-Formyl-2,4-dimethylcyclohexanone	46	(234)
1-Hydrindone	Methyl benzoate	α-Benzoyl-1-hydrindone	0	(388)
1-Hydrindone	Phenyl benzoate	α-Benzoyl-1-hydrindone	80	(388)
1-Tetralone	Methyl benzoate	α-Benzoyl-1-tetralone	0	(388)
1-Tetralone	Phenyl benzoate	α-Benzoyl-1-tetralone	46	(388)
Camphor	Ethyl formate	α-Formylcamphor	—	(742)
	Phenyl benzoate	α-Benzoylcamphor	11	(388)
2-Acetylcamphane	Ethyl benzoate	2-Benzoylacetylcamphane	Poor	(740)
Acetophenone	Ethyl propionate	α-Propionylacetophenone	55	(552, 794)
	Ethyl *n*-butyrate	α-*n*-Butyrylacetophenone	42	(552)
	Ethyl *n*-valerate	α-*n*-Valerylacetophenone	40	(552)
	Phenyl 2-ethylhexanoate	4-Ethyl-1-phenyl-1,3-octanedione	43	(570)
	Ethyl phenylacetate	Benzoylphenacylmethane	—, 19†	(60, 796)
	Ethyl phenoxyacetate	Benzoylphenoxyacetylmethane	60	(629)
	Ethyl benzoate	Dibenzoylmethane	70, 71†	(552, 904)
	Ethyl *o*-methoxybenzoate	2-Methoxydibenzoylmethane	51‡	(126)
	Ethyl *m*-methoxybenzoate	3-Methoxydibenzoylmethane	28‡	(126)
	Ethyl *p*-methoxybenzoate	4-Methoxydibenzoylmethane	45	(552)
	Ethyl 3,4,5-trimethoxybenzoate	3,4,5-Trimethoxydibenzoylmethane	21‡	(126)
	Ethyl terephthalate	4-Carbethoxydibenzoylmethane	—	(792)
	Phenyl cinnamate	α-Cinnamoylacetophenone	15–29	(393)
	Ethyl 1,2,2,3-tetramethylcyclopentane-1-carboxylate	1,2,2,3-Tetramethyl-1-benzoylacetylcyclopentane	Low	(741)
	Ethyl 2-furoate	Benzoyl-2-furoylmethane	87	(375)
4-Methoxyacetophenone	Ethyl benzoate	4-Methoxydibenzoylmethane	88	(126)
	Ethyl *m*-methoxybenzoate	3,4′-Dimethoxydibenzoylmethane	26‡	(126)
	Ethyl anisate	Dianisoylmethane	50	(854)
	Ethyl veratrate	3,4,4′-Trimethoxydibenzoylmethane	—	(126)
3,4-Dimethoxyacetophenone	Ethyl anisate	3,4,4′-Trimethoxydibenzoylmethane	—	(126)
4-Bromoacetophenone	Ethyl acetate	4-Bromobenzoylacetone	50–80	(48)

TABLE 1—*Continued*

KETONE	ESTER	PRODUCT	YIELD*	REFERENCES
			per cent	
α-Methoxyacetophenone	Phenyl propionate	α-Methoxy-α-propionylacetophenone	25	(628)
	Phenyl benzoate	α-Methoxydibenzoylmethane	26	(628)
α-Phenoxyacetophenone	Phenyl propionate	α-Phenoxy-α-propionylacetophenone	50‡	(628)
	Phenyl benzoate	α-Phenoxydibenzoylmethane	59	(628)
Propiophenone	Methyl benzoate	α-Benzoylpropiophenone	0	(388)
	Phenyl benzoate	α-Benzoylpropiophenone	53	(388)
	Ethyl *o*-methoxybenzoate	α-Anisoylpropiophenone	0	(126)
4-Methoxypropiophenone	Ethyl benzoate	α-Anisoylpropiophenone	60	(126)
1-Methoxy-2-propionaphthone	Ethyl propionate	Methyl(1-methoxy-2-naphthoyl)propionylmethane	16	(397)
2-Acetylfuran	Ethyl acetate	Acetyl-2-furoylmethane	4	(375)
	Ethyl isovalerate	Isovaleryl-2-furoylmethane	4	(375)
	Ethyl caproate	Caproyl-2-furoylmethane	2	(375)
	Ethyl benzoate	Benzoyl-2-furoylmethane	5	(375)
2-Acetylthiophene	Ethyl acetate	Acetyl-2-thenoylmethane	81, 57†	(374)
	Ethyl propionate	Propionyl-2-thenoylmethane	62, 49†	(374)
	Ethyl *n*-butyrate	*n*-Butyryl-2-thenoylmethane	62, 37†	(374)
	Ethyl isobutyrate	Isobutyryl-2-thenoylmethane	49, 30†	(374)
	Ethyl caproate	Caproyl-2-thenoylmethane	69, 42†	(374)
	Ethyl benzoate	Benzoyl-2-thenoylmethane	58, 45†	(374)
	Ethyl *p*-chlorobenzoate	*p*-Chlorobenzoyl-2-thenoylmethane	48	(800)
	Ethyl anisate	Anisoyl-2-thenoylmethane	19	(800)
	Ethyl 2-thiophenate	Di(2-thenoyl)methane	64	(374)
	Ethyl 2-furoate	2-Furoyl-2-thenoylmethane	75	(375)
	Methyl nicotinate	Nicotinoyl-2-thenoylmethane	59	(555)
	Methyl isonicotinate	Isonicotinoyl-2-thenoylmethane	65	(555)

* Yields given to nearest per cent.

† Lithium amide used as the base; in all other cases sodium amide was used.

‡ Yield based on copper salt.

C. THE CARBONATION AND CARBETHOXYLATION OF KETONES

The sodium derivatives of a number of aliphatic and aromatic ketones have been carbonated to give the sodium salts of β-keto acids, which, after acidification, have been esterified to β-keto esters in fair to good yields (551, 553). The following reaction is typical.

$$C_6H_5COC_3H_7\text{-}n \xrightarrow{NaNH_2} (C_6H_5COCHC_2H_5)^-Na^+ \xrightarrow[(3)\ CH_2N_2]{(1)\ CO_2,\ (2)\ H^+} C_6H_5COCH(C_2H_5)COOCH_3$$

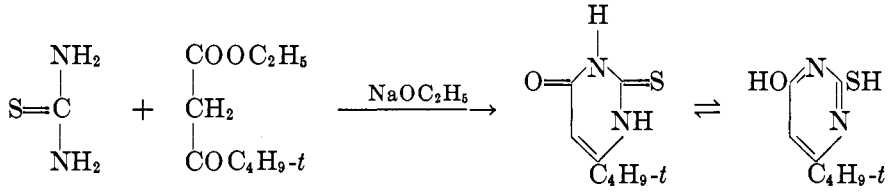
Methyl α-benzoyl-*n*-butyrate (61%) (551)

The sodium derivatives of 1-indanone (884) and of the bicyclic ketones camphor (696), 4-methylcamphor (637), isofenchone (667, 743), and verbanone (514) have been carbonated to give β-keto acids.

A variety of ketones have also been carbethoxylated with diethyl carbonate by Levine and Hauser (553) to give good yields of β-keto esters in a two-step process. Thus, ethyl isovalerylacetate was prepared in 65 per cent yield from methyl isobutyl ketone. This method has been successfully extended by other

$$(CH_3)_2CHCH_2COCH_3 + (C_2H_5O)_2O \xrightarrow{NaNH_2} (CH_3)_2CHCH_2COCH_2COOC_2H_5 + C_2H_5OH$$

workers (184, 445, 452, 583, 902). Several of these β-keto esters have been condensed with thiourea to give thiouracils in good yields (20, 24).



(43%) (20)

D. ALKYLATIONS

A large number of ketones have been alkylated with a variety of alkylating agents. However, since most of these syntheses involve extensions of the work of Haller and Bauer (368, 369), which was discussed at length in an earlier review (83, page 108), only a few specific examples will be given.

1. Aliphatic and aromatically substituted aliphatic ketones

Several papers (37, 136, 230, 493, 638, 641, 861, 886) have appeared in this area.

$$C_2H_5COC_2H_5 \xrightarrow[(2)\ CH_2{=}CHCH_2Br]{(1)\ NaNH_2} C_2H_5COCH(CH_3)CH_2CH{=}CH_2$$
(56%) (230)

$$C_6H_5CH_2COCH_3 \xrightarrow[(2)\ ClCH_2CH_2N(CH_3)_2]{(1)\ NaNH_2} CH_3COCH(C_6H_5)CH_2CH_2N(CH_3)_2$$
(57%) (886)

Vavon and Conia (861) have reported that while benzylacetone could not be alkylated with benzyl bromide in the presence of sodium amide, a 60 per cent yield of α,α-dibenzylacetone was obtained when sodium *tert*-amylate was used as the condensing agent.

2. Acetophenone, α-substituted acetophenones, and related compounds

Acetophenone (122), α-monosubstituted acetophenones (25, 105, 129, 154, 159, 176, 185, 278, 815, 831, 889), α,α-disubstituted acetophenones (6, 10, 156, 159, 160, 162, 163, 169, 171, 172, 335, 600–602, 731, 778, 848, 869), and 2-isobutyrylthiophene (164) have been alkylated with alkyl halides (25, 105, 129, 154, 162, 164, 176, 185, 307, 601, 778, 848, 869), β-phenylethyl halides (160), benzyl halides (2, 25, 156, 163, 169, 600), 1- and 2-naphthylmethyl halides (171, 172), cycloalkenyl halides (159, 889), cyclohexylmethyl halides (602), polymethylene dihalides (4), and dialkylaminoalkyl halides (278, 731, 815, 831).

A number of ketones of the type $C_6H_5CORR'CH_2Ar$ (Ar = an aromatic group; R and R′ = alkyl groups) have been prepared (600) by treating the sodium derivatives of α,α-disubstituted acetophenones with benzyl and nuclear-substituted benzyl halides.

$$C_6H_5COCHRR' \xrightarrow[(2)\ ArCH_2Cl]{(1)\ NaNH_2} C_6H_5COCRR'CH_2Ar$$

Eisleb (278) claims that the condensation of the sodium derivative of desoxybenzoin with β-diethylaminoethyl chloride gives an 80 per cent yield of γ-benzoyl-γ-phenyl-N,N-diethylpropylamine (II). However, a reinvestigation of this reaction (815) has shown that a mixture of II and its isomeric ether, β-diethylaminoethoxystilbene (III) is formed.

$$RCOCH_2R + NaNH_2 \rightarrow NH_3 + Na^+(\underset{A}{RCO\bar{C}HR} \leftrightarrow \underset{B}{RC(O^-){=}CHR})$$

$$A + \underset{I}{ClCH_2CH_2N(C_2H_5)_2} \rightarrow NaCl + \underset{II}{RCOCHRCH_2CH_2N(C_2H_5)_2}$$

$$B + I \rightarrow NaCl + \underset{III}{RC(OCH_2CH_2N(C_2H_5)_2){=}CHR}$$

R = C_6H_5.

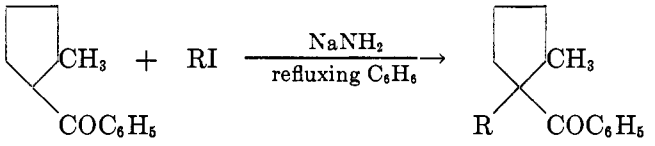
The sodium derivative of propiophenone has been alkylated with 3-chlorocyclopentene to give α-methyl-α-(Δ^2-cyclopentenyl)acetophenone (159). Sodioisobutyrophenone has been alkylated with a number of polymethylene dihalides to give diketones (4).

$$C_6H_5COCH(CH_3)_2 \xrightarrow{NaNH_2} (C_6H_5COC(CH_3)_2)^-Na^+$$
IV

$$2IV + Br(CH_2)_nBr \rightarrow C_6H_5COC(CH_3)_2(CH_2)_nC(CH_3)_2COC_6H_5 + 2NaBr$$

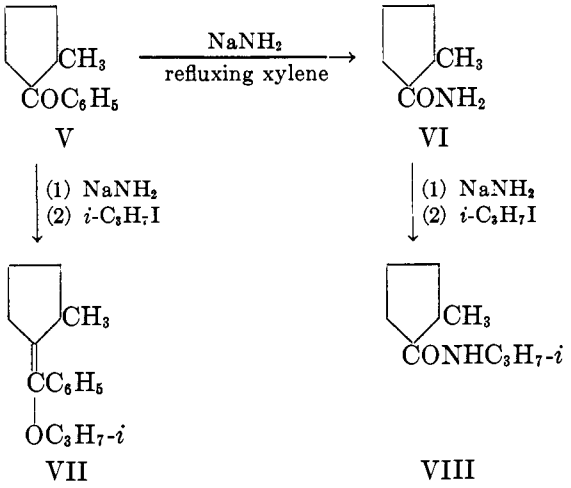
n = 3 to 10.

Wash, Shive, and Lochte (869) have studied the alkylation of phenyl 2-methylcyclopentyl ketone. In an attempt to increase the yields of products, these reactions were repeated in refluxing xylene. However in no case was the expected



R	CH_3	C_2H_5	n-C_3H_7	i-C_3H_7
Per cent yield	49	56	27	26

ketone obtained. Instead, as indicated below for the case when isopropyl iodide was the alkylating agent, three unexpected products, VI, VII, and VIII, were isolated. Compound VI, which is produced by the cleavage of V by sodium amide, is alkylated on the amide nitrogen atom to give VIII. Alkylation of the

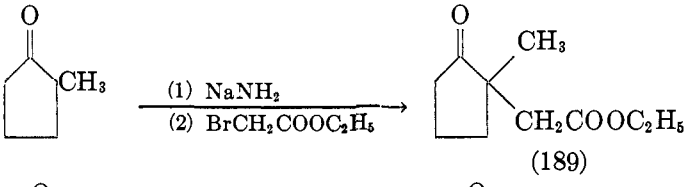


enol form of V gives VII. When these reactions are effected in refluxing toluene, a mixture of the normal and abnormal products results.

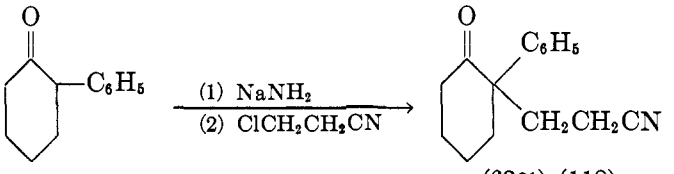
3. Cyclic ketones, including cyclopentanones, cyclohexanones, and related compounds

Cyclopentanones (189, 233, 516, 626, 839), cyclohexanones (7, 100, 118, 119, 138, 270–272, 432, 515, 533, 650, 653, 659, 699, 751, 765), cyclohexenones (421, 422, 431, 433), tetralones (51, 52, 54, 890, 902), ketotetrahydrophenanthrenes (882, 883), and 1-indanone (222) have been alkylated with alkyl halides (7, 100, 222, 270, 271, 431–433, 516, 533, 650, 659, 751), benzyl halides (218, 699), β-phenylethyl halides (421, 422, 515), cycloalkenyl halides (272, 890), dialkylaminoalkyl halides (51, 52, 54, 138, 902), haloesters (119, 189, 626, 839, 882, 883), halonitriles (118, 765), and alkanesulfonic esters (653).

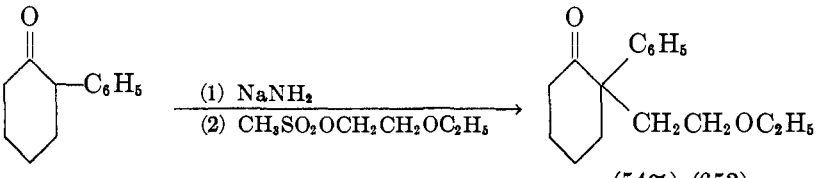
The following examples are typical.



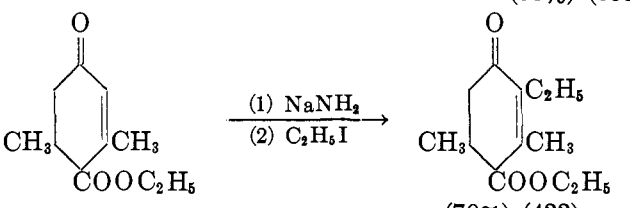
(189)



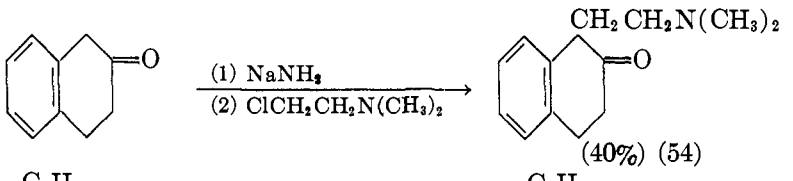
(63%) (118)



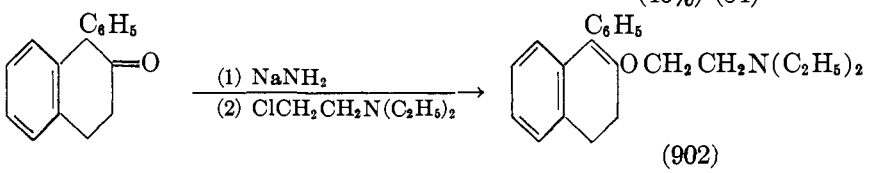
(54%) (653)



(70%) (433)



(40%) (54)

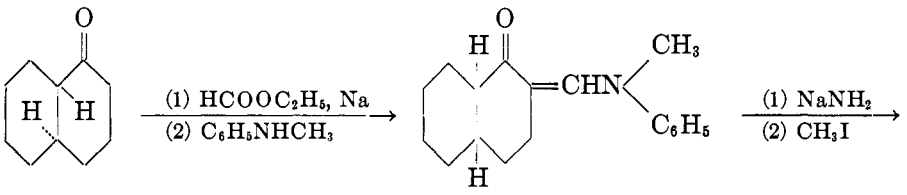


(902)

It is interesting to note, as shown above, that while 2-tetralone is alkylated on carbon by 2-dimethylaminoethyl chloride, 1-phenyl-2-tetralone is alkylated on oxygen by 2-diethylaminoethyl chloride to give an enol ether.

4. Introduction of angular methyl groups

Several reports have been published (103, 104, 106, 460, 461) concerning the introduction of angular methyl groups into decalones and hydrindanones. Thus, starting with *trans*-1-decalone (I), a mixture of *cis*- and *trans*-9-methyl-1-decalones (IV) was obtained in an overall yield of 55 per cent (106).

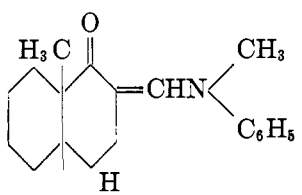


I

trans-1-Decalone

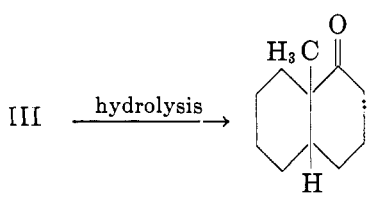
II

cis- and *trans*-2-Methanilinomethylene-1-decalone



III

cis- and *trans*-9-Methyl-2-methanilinomethylene-1-decalone



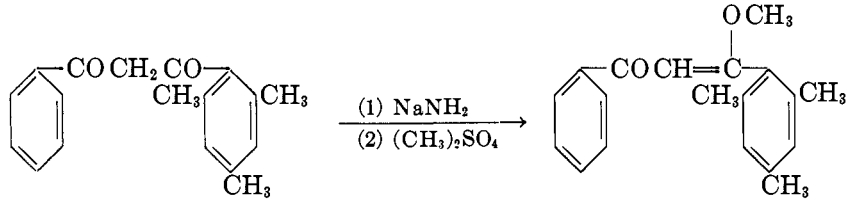
IV

cis- and *trans*-9-Methyl-1-decalone

5. Other ketone alkylations

The sodium derivatives of 2,2′-diketobicyclopentyl (442) and of the bicyclic ketones isofenchone (846), α-isocamphenilone (636), and camphor (723) have been methylated with methyl iodide.

When the β-diketone 2,4,6-trimethyldibenzoylmethane is treated successively with sodium amide and dimethyl sulfate, *O*-alkylation occurs to give a 66.8 per cent yield of 1-mesityl-1-methoxy-3-phenyl-1-propen-3-one (301).



Attempts to alkylate 6-methoxy-3-coumaranone with isopropyl iodide in the presence of sodium amide failed (526).

E. CLEAVAGE OF NON-ENOLIZABLE ARYL ALKYL KETONES AND RELATED COMPOUNDS

The cleavage of ketones by the alkali amides, which was discussed in the earlier reviews (83, page 124; 84, page 449), has been extended considerably (2, 4, 11, 12, 13, 15, 18, 34, 105, 158, 159, 160, 162, 163, 169, 170, 171, 172, 185, 292, 293, 296, 544, 600, 601, 614, 661, 729, 760, 778, 798, 846, 869).

The reaction of non-enolizable ketones with alkali amides may take two paths. The first course occurs when the ketone and alkali amide are heated in the

$$RCOR' \xrightarrow{NaNH_2} \begin{cases} \xrightarrow{I} RH + R'H + RCONH_2 + R'CONH_2 \\ \xrightarrow{II} RH + R'H + Na_2CN_2 + H_2O \end{cases}$$

presence of aromatic hydrocarbons such as toluene, the xylenes, or *p*-cymene, while the second course takes place when the ketone and alkali amide are fused.

The first set of conditions is most often used; when an aryl *tert*-alkyl ketone is treated in this way, the major products formed are an aromatic hydrocarbon and an aliphatic amide.

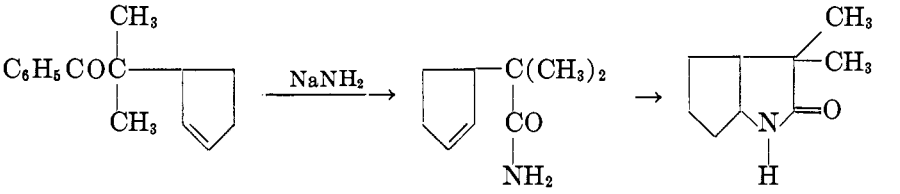
$$C_6H_5CO\,C(CH_3)_2\,C_{10}H_{21}\text{-}n \xrightarrow{NaNH_2} C_6H_6 + H_2NCO\,C(CH_3)_2\,C_{10}H_{21}\text{-}n$$
(48%) (105)

Treatment of the completely aromatic ketone 3,4-diphenylbenzophenone with sodium amide in boiling *p*-cymene gave 1,2-diphenylbenzene (70 per cent) and 3,4-diphenylbenzoic acid (7 per cent) (13). This reaction probably involves the cleavage of the starting ketone to benzene and 3,4-diphenylbenzamide. The amide then hydrolyzes as the reaction mixture is processed to give 3,4-diphenylbenzoic acid, part of which is isolated but most of which is decarboxylated to 1,2-diphenylbenzene.

The fusion of benzopinacolone with sodium amide at 200°C. gives benzene and an 81 per cent yield of triphenylmethane (course II; R = C_6H_5 and R′ = $(C_6H_5)_3C$), while the reaction of Michler's ketone with sodium amide at 180°C. gives an 85 per cent yield of dimethylaniline (296).

Buu-Hoï and Cagniant (159) have found that if α,α,α-trialkylacetophenones in which one of the alkyl radicals contains the grouping $-\overset{|}{C}=CH\overset{|}{C}-$ are treated

with sodium amide, heterocyclic nitrogen compounds are formed. The following case is typical. While none of the amide IV was isolated, it appears reasonable



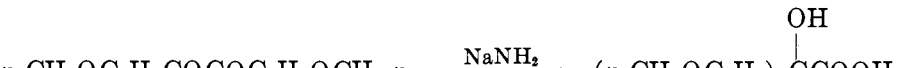
III IV V

α, α-Dimethyl-α-(Δ²-cyclopentenyl)acetophenone

3, 3-Dimethyl-4, 5-trimethylene-2-pyrrolidone

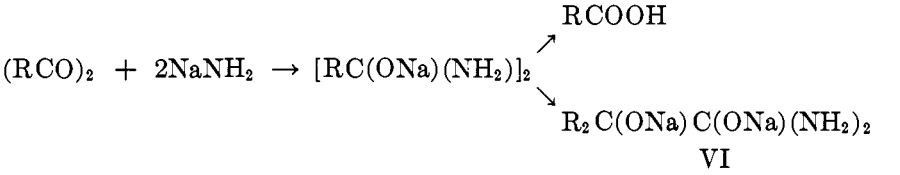
to assume that III is cleaved to IV, which then undergoes intramolecular addition of the amide amino group to the double bond of the cyclopentene ring to give V.

Oliverio (673) has attempted to prepare anisilic, veratrilic, and piperilic acids by a sodium amide-effected benzilic acid rearrangement of the corresponding 1,2-diketones. With anisil the reaction took the expected course. However, when veratril and piperil were treated with sodium amide, the expected re-



Anisil

arranged products were not obtained. Instead, veratric acid and 3,4,3′,4′-tetramethoxybenzophenone were isolated from the former and piperonylic acid and 3,4,3′,4′-bis(methylenedioxy)benzophenone were obtained in the latter reaction. The following scheme, where R represents the 3,4-dimethoxyphenyl or the 3,4-methylenedioxyphenyl radical, shows how these products might be formed.



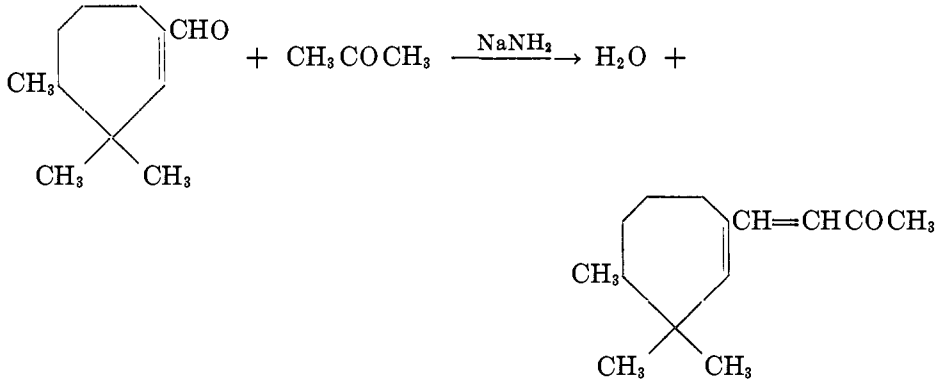
VI

F. ALDOL-TYPE CONDENSATIONS

Acenaphthenone (337), 1-acetylcyclohexene (464), and pulegone (588) have been self-condensed by reaction with sodium amide. Vavon and Conia (860, 861) report that attempts to alkylate cyclohexanone, 2-methylcyclohexanone, and 4-methylcyclohexanone failed in the presence of sodium amide, since the ketones are self-condensed more rapidly than they are alkylated.

Birch (100) has obtained 6-piperonylidene-2,2-dimethylcyclohexanone by treating piperonal with 2,2-dimethylcyclohexanone in the presence of sodium

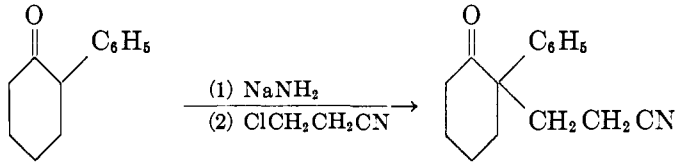
amide. Acetone has been condensed with 1-formyl-3,3,4-trimethylcycloheptene (744).



G. MICHAEL ADDITIONS

The Michael additions between cinnamic esters and ketone anions have already been discussed in Section VIII,A of this review.

The reaction of sodio-2-phenylcyclohexanone with β-chloropropionitrile to give 2-(β-cyanoethyl)-2-phenylcyclohexanone in 63 per cent yield (118) appears to be an alkylation reaction. However, Barkley and Levine (49) have shown that reactions of this type involve interaction of the ketone anion and β-chloro-



propionitrile to give acrylonitrile and the ketone, which then react in a Michael addition to give cyanoethylated products. These workers have studied the reactions of several unsymmetrical dialkyl ketones with β-chloropropionitrile and found that the cyanoethyl groups are introduced at the more highly substituted α-carbon atom of the ketones. The case of methyl ethyl ketone is typical.

$$CH_3COCH_2CH_3 + NaNH_2 \longrightarrow$$

$$(CH_3COCHCH_3 \rightleftharpoons CH_2COCH_2CH_3)^-Na^+ \xrightarrow{ClC_2H_4CN}$$

$$\underset{\text{I}}{CH_2{=}CHCN} + \underset{\text{II}}{CH_3COCH_2CH_3} + NaCl$$

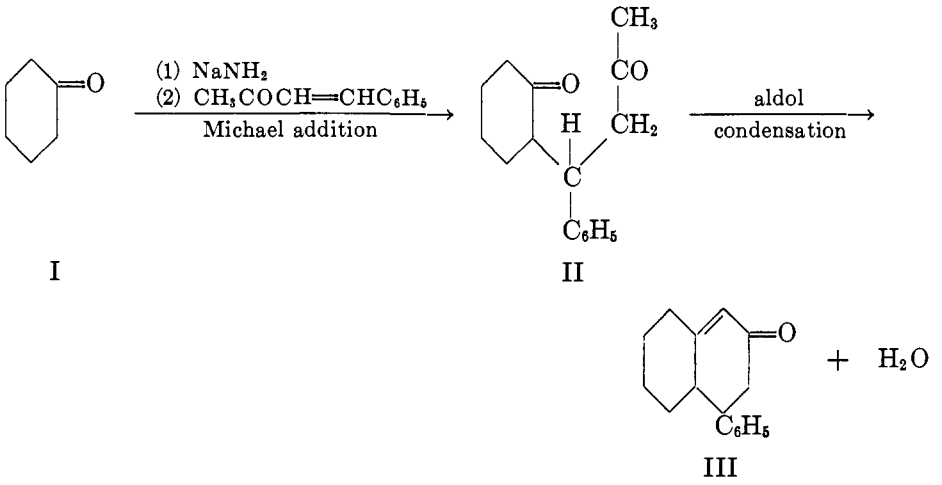
$$I + II \rightarrow \underset{(6\%)}{CH_3COCH(CH_3)C_2H_4CN} + \underset{(47\%)}{CH_3COC(CH_3)(C_2H_4CN)_2}$$

H. REACTIONS INVOLVING BOTH ALDOL CONDENSATIONS AND MICHAEL ADDITIONS

Cyclic ketones including cyclohexanone (720), 2-methylcyclohexanone (364), and certain tetralones (151, 152, 394, 467, 692, 693, 720) have been condensed

with α,β-unsaturated ketones such as ethyl ethynyl ketone (364), methyl styryl ketone (720), methyl 1-cyclopentenyl ketone (151, 152, 394, 693, 720), and methyl (692, 720) and ethyl (467) 1-cyclohexenyl ketones in the presence of sodium amide.

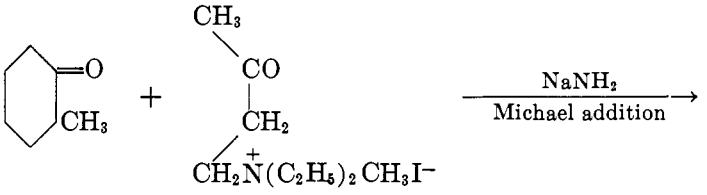
All these reactions are quite similar, and the condensation of cyclohexanone with methyl styryl ketone may be regarded as typical (720). The anion of I probably reacts with methyl styryl ketone in a Michael addition to give II, which undergoes an internal aldol condensation with the subsequent elimination of water to give III, 2-keto-4-phenyl-$\Delta^{1,9}$-octalin, in 43 per cent yield.



I II III

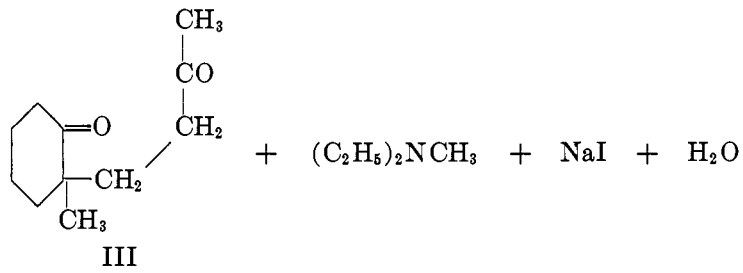
I. THE ROBINSON MODIFICATION OF THE MANNICH REACTION

The Robinson modification of the Mannich reaction[3] (51, 232, 241, 338, 364, 580, 596, 733) is closely related to the synthesis just discussed. The use of sodium amide to prepare 2-keto-10-methyl-$\Delta^{1,9}$-octalin from 2-methylcyclohexanone (I) in an overall yield of 38 per cent illustrates the method. It is probable that sodium amide converts II to methyl vinyl ketone, which then reacts with I through the reaction sequence Michael addition, internal aldol condensation, and dehydration to give V.

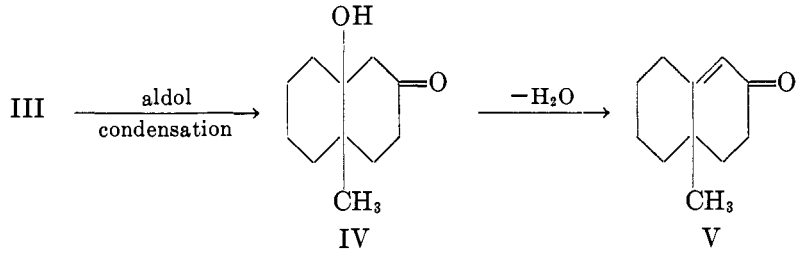


I II

[3] For a review of the Mannich reaction, see Chapter 10 by F. F. Blicke in Volume 1 of *Organic Reactions*, John Wiley and Sons, Inc., New York (1942).



III



IV V

J. OTHER REACTIONS OF KETONES, INCLUDING KETENE

The sodium derivative of cyclohexanone has been chlorinated with ethyl hypochlorite to give 2-chlorocyclohexanone (623).

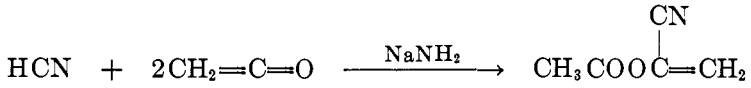
Ethyl 6-benzoylhexanoate is converted to 2-benzoylcyclohexanone in 60 per cent yield when treated with sodium amide (51).

Bradley (124) has reported that the anion of piperidine, prepared from piperidine and sodium amide, reacts with mesobenzanthrone to give a mixture of 2-piperidinomesobenzanthrone and 2-hydroxymesobenzanthrone.

When a solution of α-hydrindone in concentrated sulfuric acid is treated with sodium amide in the cold, a 55 per cent yield of 3,4-dihydrocarbostyril is obtained (834).

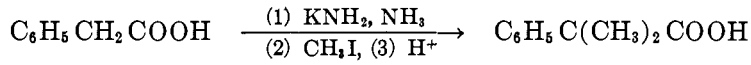
The isovaleryl ester of cyclohexanone oxime is obtained in 94 per cent yield when the sodium salt of the oxime, prepared by its reaction with sodium amide, is treated with isovaleryl chloride (246).

Johnston and Newton (462) have treated ketene with hydrogen cyanide and sodium amide at $-3°$C. in an acetic anhydride medium and have obtained 1-cyanovinyl acetate. The overall reaction follows.



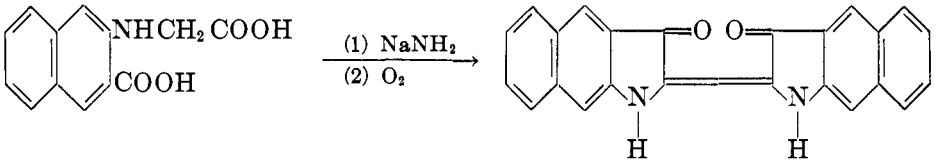
IX. Acids and Anhydrides

Birch (102) has dialkylated phenylacetic and 1-naphthylacetic acids with methyl iodide in the presence of potassium amide in liquid ammonia.



When hydrocamphorylmalonic or hydrocamphorylacetic acid is heated with sodium amide, a small amount of homocamphor is obtained (150).

When 3-carboxy-2-naphthylaminoacetic acid is fused with sodium amide (258, 288) a 15–20 per cent yield of 2,3,2′,3′-naphthindigo is obtained.



Metallic salts (294, 295) of formic, acetic, propionic, and benzoic acids react with sodium amide to give the monosodium salt of cyanamide. Freidlin (291)

$$2RCOOM + 2NaNH_2 \rightarrow NaHCN_2 + M_2CO_3 + NaOH + 2RH$$

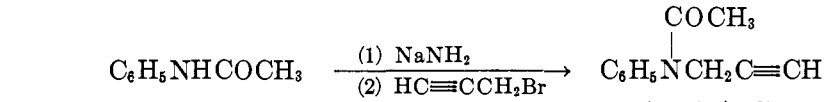
has reported that heating potassium formate with 2–4 per cent of its weight of sodium amide at 240°C. results in an 80 per cent conversion of the formate to the oxalate.

Beck (59) has found that sodium amide reacts with acetic anhydride in a 1:1 molar ratio to give an unstable addition compound, which is readily decomposed by water. This compound is probably formed by the addition of sodium amide across one of the carbonyl groups of the anhydride.

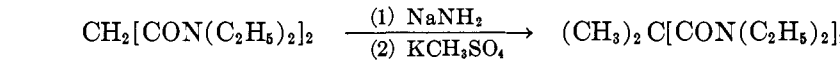
X. Amides

A. Alkylation

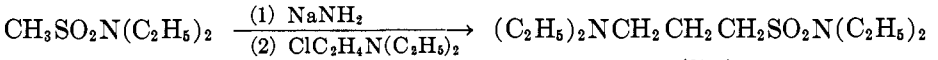
A large number of aliphatic, aromatic, carbocyclic, and heterocyclic amides (302, 304, 309, 311, 312, 313, 315, 320, 323, 324, 326, 332, 359, 361, 503, 505, 506, 576, 578, 808, 892) have been alkylated with a variety of alkylating agents, and several alkyl- and arylsulfonamides have been alkylated (278, 279, 455, 504, 506) and heterylated (208). The following examples are typical.



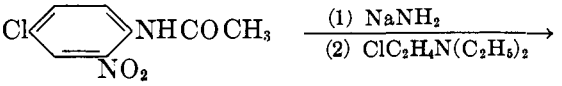
(35%) (892)

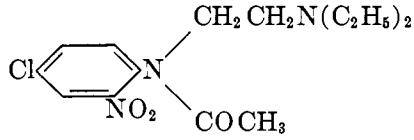


(313)

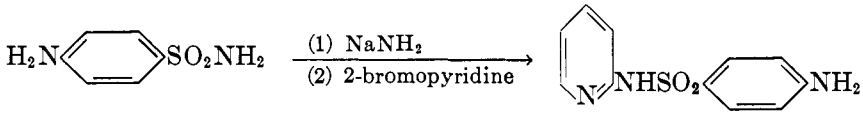


(278)





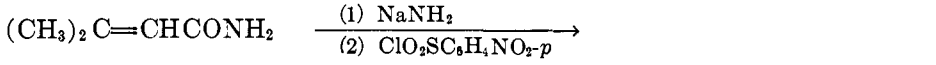
(67.5%) (503)



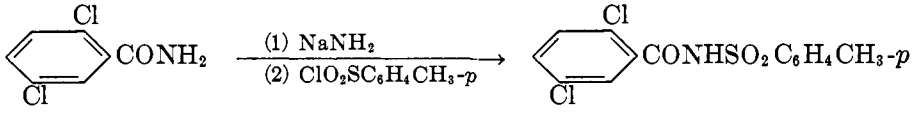
(208)

B. ACYLATION

A number of aliphatic and aromatic amides (307, 314 316–318, 321, 330, 331, 443, 577) have been acylated with several aromatic sulfonyl halides to give the corresponding sulfonamides.



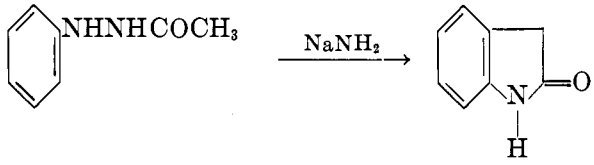
(318)



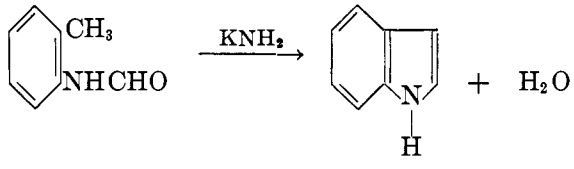
(317)

C. CYCLIZATION REACTIONS

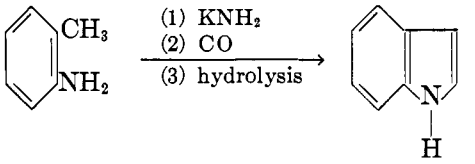
Oxindole has been prepared (827) from the reaction of sodium amide with acetic acid phenylhydrazide.



Tyson (*cf.* 83, page 134, and 863) has found that indole is formed in fair yield by the reaction of *o*-formotoluidide with potassium amide (849) or the sodium

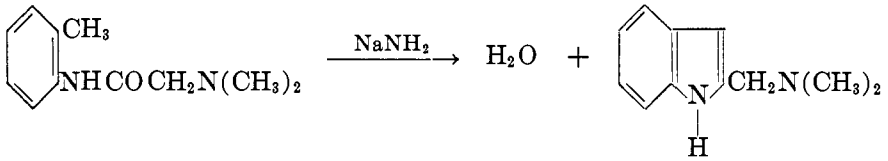


or potassium derivative of *o*-methoxyaniline (850). Indole is also prepared in high yield (82 per cent) (850) by the reaction of the potassium salt of *o*-toluidine



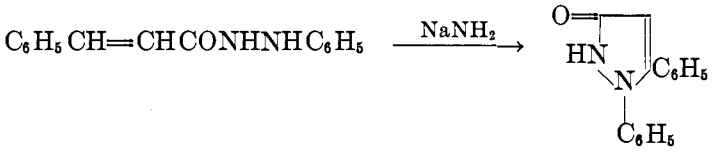
(82%) (850)

with carbon monoxide in an autoclave, probably via the intermediate formation of *o*-formotoluidide. Kornfeld's synthesis of 2-dimethylaminomethylindole (518) is closely related to the Verley–Tyson synthesis of indole.



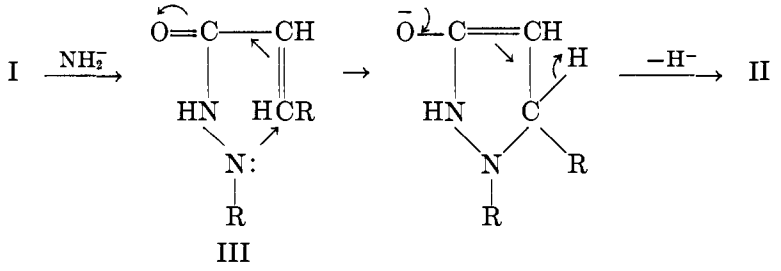
(66%) (518)

Stanek (826) has found that the phenylhydrazides of cinnamic acid (I) and α-methylcinnamic acid are cyclized by sodium amide to give 1,5-diphenyl-3-pyrazolone (II) and 1,5-diphenyl-4-methyl-3-pyrazolone, respectively. A pos-



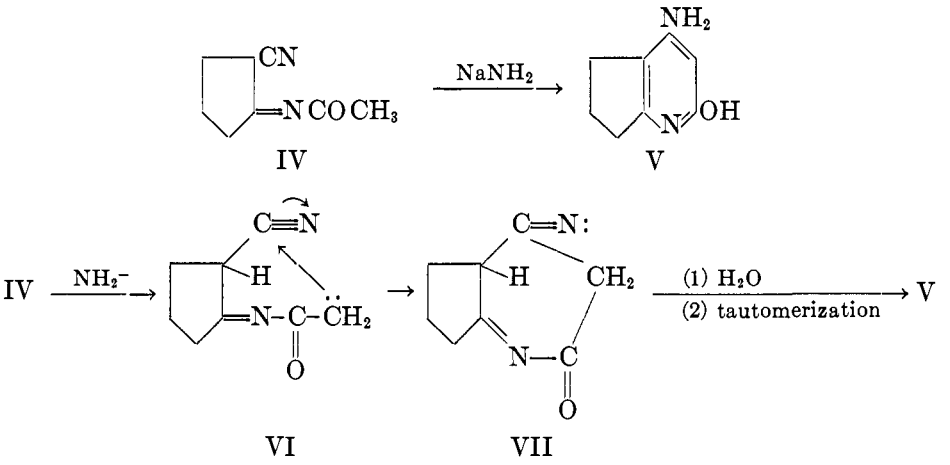
I II

sible scheme for the conversion of I to II involves the formation of anion III, followed by cyclization and ejection of a hydride ion.



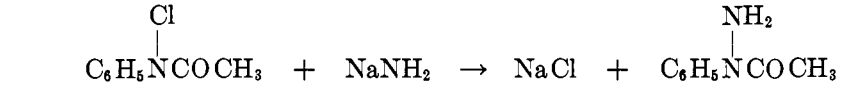
R = C_6H_5.

Schroeder and Rigby (761) have prepared 4-amino-2-hydroxy-6,7-dihydropyrindine (V) in 96 per cent yield by the reaction of 2-acetylimino-1-cyanocyclopentane (IV) with sodium amide. Compound V may be formed by conversion of IV to its anion, VI, followed by intramolecular cyclization to VII, which on hydrolysis tautomerizes to V.



D. OTHER REACTIONS OF AMIDES

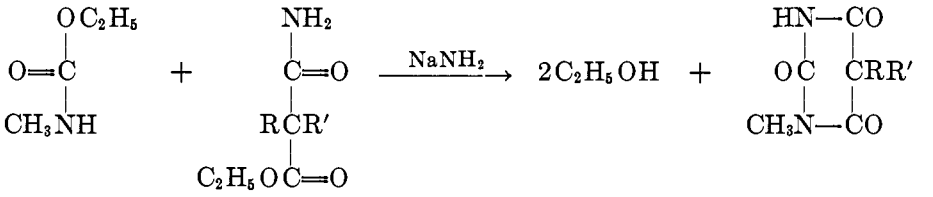
The reactions of halogenated amides with sodium amide have been studied (264, 593, 783). Thus, Short (783) has prepared *N*-aminoacetanilide in 80 per cent yield by the reaction of sodium amide with *N*-chloroacetanilide. However, if the halogen is bonded to carbon rather than to nitrogen, as in 9-biphenylene-



chloroacetamide (593), it is not replaced by the amino group on reaction with sodium amide.

Upon treatment with sodium amide in liquid ammonia, *cis*-hexahydro-*o*-toluamide is converted to its *trans* isomer (598).

The methyl urethan of ethyl alcohol has been condensed with the half-amide half-ester of methyl(1-cyclohexenyl)malonic acid in the presence of sodium amide to give the corresponding barbituric acid (841).



R = methyl; R′ = 1-cyclohexenyl.

XI. Nitriles

A. Alkylations, Arylations, and Heterylations

1. Aliphatic nitriles

Aliphatic nitriles have been condensed with alkyl halides (81, 105, 157, 265, 410, 519, 643, 762, 817), alkyl *p*-toluenesulfonates (81), dihaloalkanes (217,

410, 665, 688, 690, 757, 758), aryl halides (81), and heterocyclic halides (822). Thus, the reaction of acetonitrile with 2-bromopyridine (822) gives di(2-pyridyl)-acetonitrile (25 per cent).

$$CH_3CN \xrightarrow[(2)\ 2\text{-}C_5H_4NBr]{(1)\ NaNH_2} (2\text{-}C_5H_4N)_2CHCN$$

When an aliphatic nitrile which has only one α-hydrogen atom is alkylated with an alkyl halide, monoalkylation occurs (e.g., 157 and 519). However, if an aliphatic nitrile which has two or three α-hydrogen atoms is treated with an alkyl halide, then, depending on reaction conditions, a number of products such as mono-, di-, and trialkylated nitriles and amidines may be formed (81, 643, 762, 817).

Paul and Tchelitcheff (688, 690) have studied the sodium amide-effected reactions of acetonitrile and dihaloalkanes and have found that the products obtained depend on several factors: (*1*) the length of the carbon chain of the dihalide, (*2*) the halogen, (*3*) the solvent, and (*4*) the molar ratio of the reactants. Thus, although 1,3-dichloropropane did not react with sodium amide and acetonitrile in an ether medium, an 8 per cent yield of pimelonitrile was isolated when dioxane was used as the solvent. The reaction of 1,3-diiodopropane with acetonitrile in ether gave a 12 per cent yield of pimelonitrile and a 38 per cent yield of allyl-acetonitrile, while in dioxane only a 13 per cent yield of pimelonitrile was obtained.

Bergstrom and Agostino (81) arylated acetonitrile by treating it with potassium amide and chlorobenzene in liquid ammonia and obtained phenylacetonitrile (31 per cent) and diphenylacetonitrile (28 per cent).

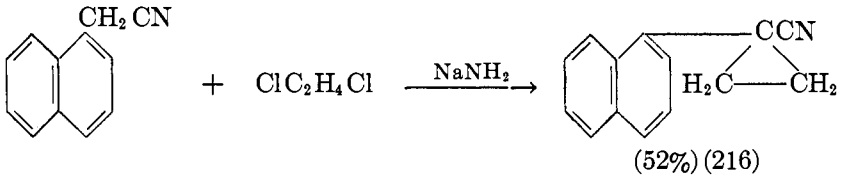
The formation of cyclic nitriles by the reaction of halonitriles with sodium amide, which was discussed earlier (83, page 139; 215) has been extended (217, 665, 757, 758). Thus, the reaction of γ-chloro-β-methylbutyronitrile with sodium amide in liquid ammonia gives a 60 per cent yield of 1-cyano-2-methylcyclopropane (217).

$$ClCH_2CH(CH_3)CH_2CN \xrightarrow{NaNH_2} \begin{array}{c} CHCN \\ / \quad \backslash \\ H_2C\text{——}CHCH_3 \end{array}$$

2. Phenylacetonitrile and related compounds

Phenylacetonitrile, nuclear-substituted phenylacetonitriles, and 1- and 2-naphthylacetonitriles have been alkylated with a number of classes of reagents such as alkyl halides (5, 69, 129, 130, 223, 390, 435, 459, 469, 534, 603, 684, 799, 824, 848), aralkyl halides (156, 159, 161, 253, 300, 645–648, 788), carbocyclic halides (1, 98, 373, 604, 855, 856, 862, 876), cyclic olefinic halides (160, 453, 454), dialkylaminoalkyl halides (71, 99, 111, 147, 213, 419, 527, 528, 567, 568, 605, 606, 735, 823, 828, 836), haloesters (40), olefinic haloethers (68, 70, 72), halonitriles (429, 430, 432), dihaloalkanes and dihaloalkenes (186, 216, 366, 377, 630, 844, 877), dialkyl sulfates (122, 140, 436), and epoxides (21). Several of these

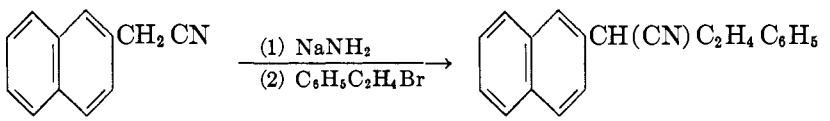
nitriles have also been heterylated (205, 247, 376, 615, 619, 806, 835, 837). A few representative examples follow.



(52%) (216)

$$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{CN} \xrightarrow[(2)\ \text{C}_2\text{H}_5\text{Br}]{(1)\ \text{NaNH}_2} p\text{-ClC}_6\text{H}_4\text{CH(CN)C}_2\text{H}_5$$

(71%) (824)



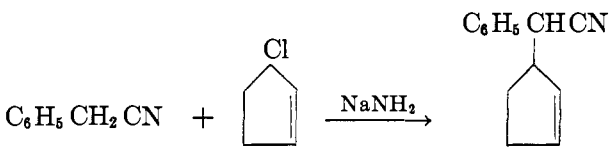
(67%) (647)

$$\text{C}_6\text{H}_5\text{CH}_2\text{CN} \xrightarrow[(2)\ \text{cyclohexyl bromide}]{(1)\ \text{NaNH}_2} \text{C}_6\text{H}_5\text{CH(CN)C}_6\text{H}_{11}$$

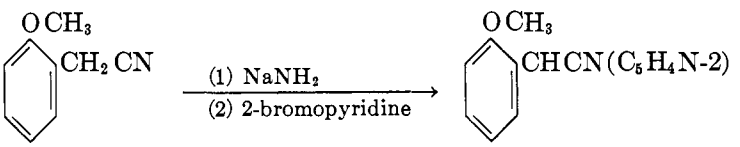
(75%) (98)

$$\text{C}_6\text{H}_5\text{CH}_2\text{CN} \xrightarrow[(2)\ \text{ClC}_2\text{H}_4\text{N(CH}_3)_2]{(1)\ \text{NaNH}_2} \text{C}_6\text{H}_5\text{CH(CN)C}_2\text{H}_4\text{N(CH}_3)_2$$

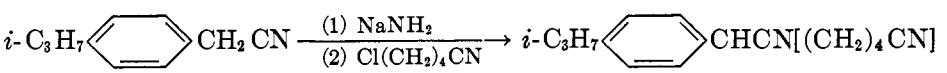
(90%) (636)



(453)

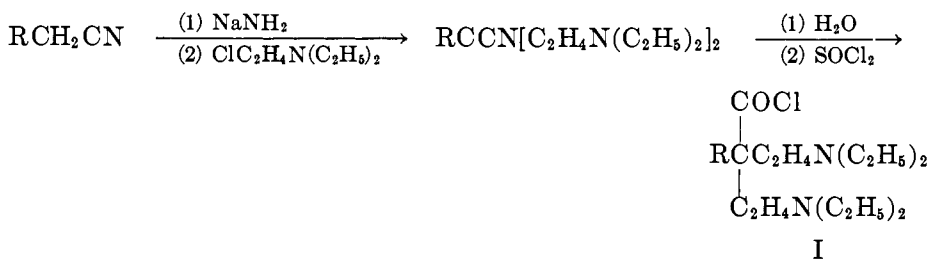


(63%) (615)

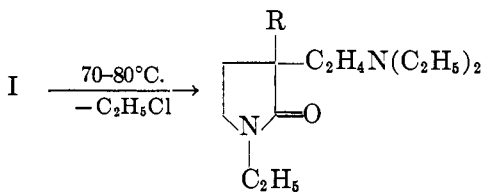


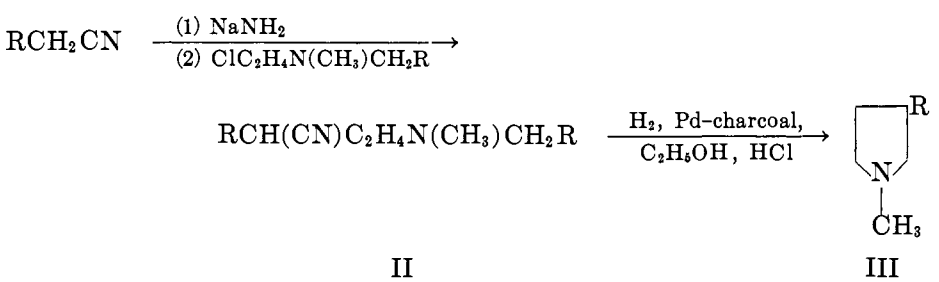
(58%) (432)

The products obtained by alkylating phenylacetonitrile with 2-dialkylaminoethyl halides have been found to be useful intermediates for the synthesis of 2-pyrrolidones (568) and 3-phenylpyrrolidines (71).



I



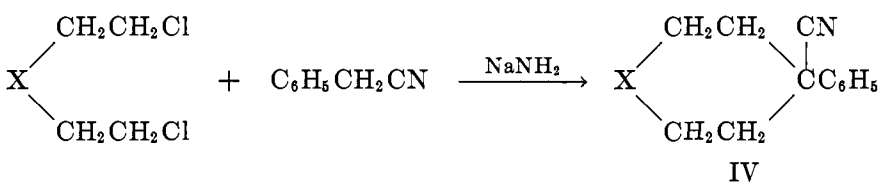


II III

R = C_6H_5.

The production of III from II appears to involve the hydrogenolysis of the benzyl group and reduction of the nitrile group of II to give a 1,4-diamine, which cyclizes with the loss of ammonia.

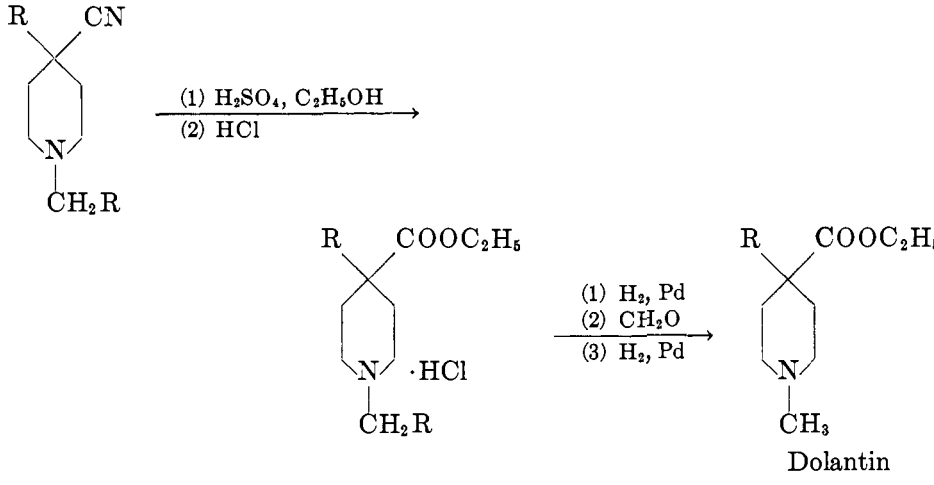
Eisleb (277, 278) and others (67, 721) have prepared six-membered heterocyclic compounds in good yields by condensing phenylacetonitrile and its nuclear-substituted derivatives with dihalides of appropriate structure. 1-Benzyl-4-cyano-4-phenylpiperidine (IV: X = $NCH_2C_6H_5$) is the key intermediate in the



IV

X = O, S, or NR, where R = CH_3, C_2H_5, $CH_2C_6H_5$, or $SO_2C_6H_5$.

synthesis of the valuable analgesic Dolantin (Demerol) (852). Six-membered carbocyclic compounds may also be made by a route similar to the Eisleb method.

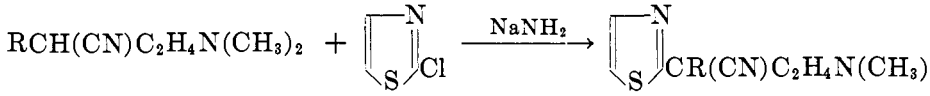


R = C_6H_5.

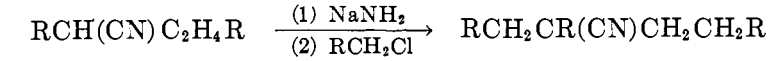
Thus, the reaction of phenylacetonitrile with 1,5-dichloro-3-dimethylaminopentane gives 1-cyano-4-dimethylamino-1-phenylcyclohexane (417).

3. Monoalkylated and monoacylated phenylacetonitriles

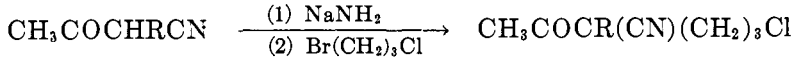
Monoalkylated and monoacylated phenylacetonitriles have been converted to trisubstituted acetonitriles by heterylation (818) and alkylation with alkyl halides (25, 535, 875, 880), aralkyl halides (54, 627), dialkylaminoalkyl halides (73, 110, 136, 147, 247, 278, 451, 453, 454, 567, 736, 738, 886), halonitriles (649), and dihaloalkanes (37, 472, 605, 807). A few examples follow.



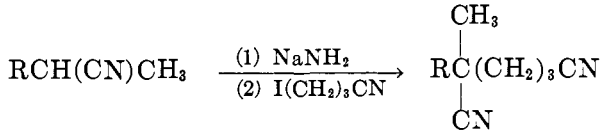
(818)



(60%) (44)



(37)



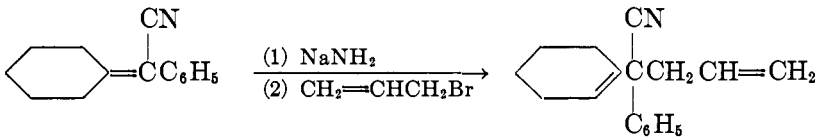
(85%) (649)

$$RCH(CN)C_6H_{13}\text{-}n \xrightarrow[(2)\ ClC_2H_4N(C_2H_5)_2]{(1)\ NaNH_2} RC(CN)(C_6H_{13}\text{-}n)[C_2H_4N(C_2H_5)_2]$$

(75%) (278)

R = C_6H_5.

There are, however, three types of alkylations which should be discussed in more detail. It has been possible to alkylate cycloalkylidenephenylacetonitriles to give alkyl-1-cycloalkenylphenylacetonitriles (453, 454, 880). Thus, Whyte and Cope (880) have alkylated cyclohexylidenephenylacetonitrile (I) with allyl bromide and obtained allyl-1-cyclohexenylphenylacetonitrile (II) (77 per cent).

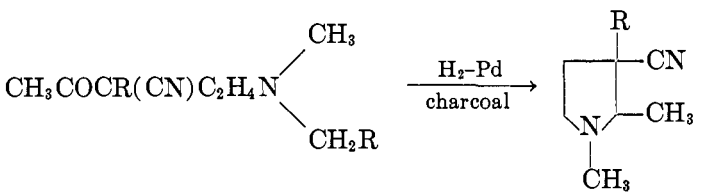


I II

It seems reasonable to believe that I is in equilibrium with 1-cyclohexenylphenylacetonitrile, which is the form alkylated to give II.

Acylphenylacetonitriles (73) have been alkylated with benzyl(2-chloroethyl)methylamine to give intermediates which have been hydrogenated to give pyrrolidine derivatives. The formation of IV from III probably involves the

$$CH_3COCHRCN \xrightarrow[(2)\ ClC_2H_4N(CH_3)CH_2R]{(1)\ NaNH_2}$$

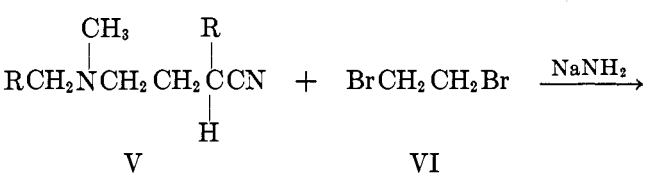


III IV

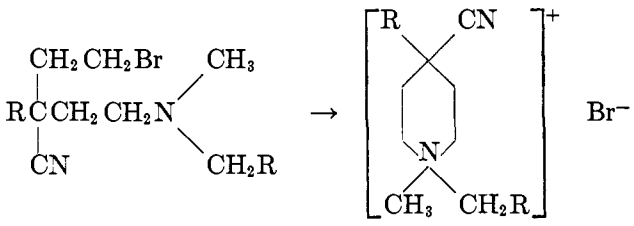
R = C_6H_5.

hydrogenolysis of the benzyl group and reduction of the carbonyl group of III to give a δ-amino alcohol, which cyclizes with loss of water.

(2-Dialkylaminoethyl)phenylacetonitriles have been alkylated with aliphatic vicinal dihalides to give piperidine derivatives (472, 605, 807). Thus, γ-(benzylmethylamino)-α-phenylbutyronitrile (V) has been alkylated with ethylene dibromide (605, 807) to give 1-benzyl-4-cyano-1-methyl-4-phenylpiperidinium bromide (VIII), probably via the intermediate formation of VII, which cyclizes.



V VI



VII VIII

R = C_6H_5.

4. Diphenylacetonitrile

Diphenylacetonitrile, nuclear-substituted diphenylacetonitriles, and 9-cyanofluorene have been alkylated with alkyl halides and certain dialkylaminoalkyl halides to give trisubstituted acetonitriles of unambiguous structure (112, 193, 269, 273, 275, 403, 448, 618, 737, 868, 887).

$$(C_6H_5)_2CHCN \xrightarrow[(2)\ ClC_2H_4N(CH_3)_2]{(1)\ NaNH_2} (C_6H_5)_2\overset{CN}{\overset{|}{C}}CH_2CH_2N(CH_3)_2$$

(92%) (112)

When the three types of nitriles listed above are alkylated with a dialkylaminoalkyl halide such as 2-chloro-1-dimethylaminopropane (I), isomeric alkylated compounds are formed (116, 347, 404, 669–671, 764, 773, 814, 873). This reaction has been studied extensively because of its importance in the synthesis of the German analgesic Amidone and compounds related to it. The German synthesis of Amidone is indicated below (852).

$$(C_6H_5)_2CHCN + \underset{\text{I}}{(CH_3)_2NCH_2\overset{Cl}{\overset{|}{C}}HCH_3} \xrightarrow{NaNH_2}$$

$$(C_6H_5)_2\overset{CN}{\overset{|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}HN(CH_3)_2$$

II

$$\text{II} \xrightarrow[(2)\ H_2O]{(1)\ C_2H_5MgBr} (C_6H_5)_2\overset{CH_2\overset{CH_3}{\overset{|}{C}}HN(CH_3)_2}{\overset{|}{C}}CO\,C_2H_5$$

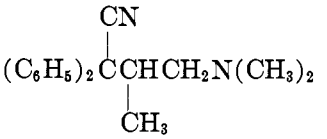
III

Amidone

Several questions arise concerning this synthesis: (*1*) How is II formed? (*2*)

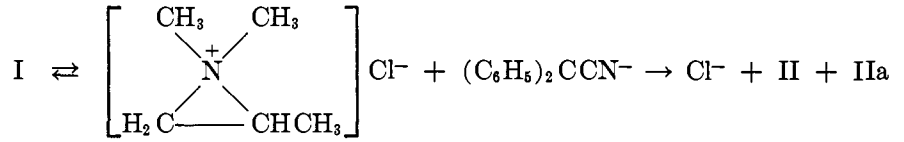
Is an isomer of II also present? (*3*) Does III represent the structure of Amidone? (*4*) Can a compound having structure III be prepared in another way?

A number of workers have been interested in the Amidone problem. It has been found (764) that the interaction of I, diphenylacetonitrile, and sodium amide actually gives rise to two isomeric nitriles. These are II, the rearranged alkylated product, and IIa, the normal alkylated product. It has been suggested (764) that I is probably in equilibrium with the ethylenimmonium ion structure (Ia)



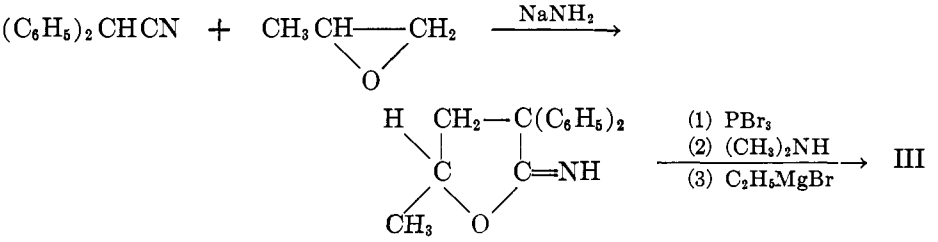
IIa

and that the reaction of the diphenylacetonitrile anion with Ia may follow two paths and give rise to a mixture of II and IIa.



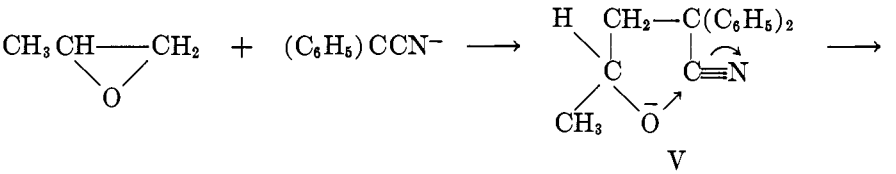
Ia

There is now no doubt that Amidone is correctly represented by structure III, since the following method of synthesis gives a compound identical with III (274). The formation of IV (2-imino-3,3-diphenyl-5-methyltetrahydrofuran)

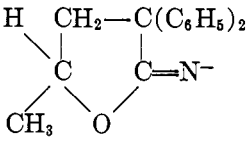


IV

and/or the corresponding lactone, α,α-diphenyl-γ-valerolactone, by the reaction of diphenylacetonitrile with propylene oxide has also been reported by other workers (35, 885). Compound IV is probably formed by the cleavage of propylene oxide by the anion of diphenylacetonitrile to give V, which cyclizes to VI, which in turn is converted to IV.



V



$\xrightarrow{H_2O}$ IV

VI

Two syntheses have been reported (790, 791) for IIa, which on reaction with ethylmagnesium bromide gives an isomer of Amidone which has been called Isoamidone or Isomethadone. One of these syntheses (790) follows:

$$(C_6H_5)_2CHCN + CH_3CH(OSO_2C_6H_4CH_3\text{-}p)CH_2Cl \xrightarrow[(2)\ (CH_3)_2NH]{(1)\ NaNH_2}$$

$$\text{IIa} \xrightarrow[(2)\ H_2O]{(1)\ C_2H_5MgBr} (C_6H_5)_2C(CH_3CHCH_2N(CH_3)_2)COC_2H_5$$

Isoamidone

B. ACYLATION

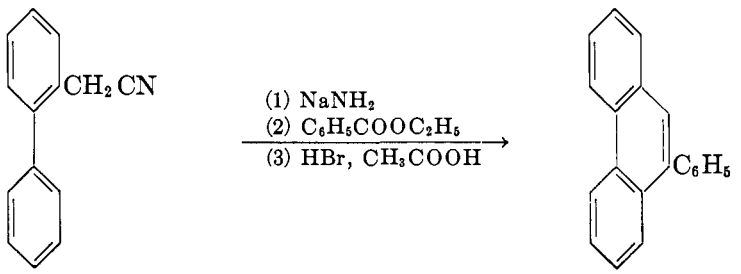
Levine and Hauser (554) have acylated and carbethoxylated nitriles. Thus, the reaction of acetonitrile, ethyl propionate, and sodium amide gave propionylacetonitrile (40 per cent), while the carbethoxylation of phenylacetonitrile with diethyl carbonate gave ethyl α-cyano-α-phenylacetate (69 per cent yield). Phenylacetonitrile has also been acylated with ethyl β-phenylpropionate in 75–80 per cent yield (739).

$$CH_3CN \xrightarrow[(2)\ C_2H_5COOC_2H_5]{(1)\ NaNH_2} C_2H_5COCH_2CN$$

$$C_6H_5CH_2CN \xrightarrow[(2)\ CO(OC_2H_5)_2]{(1)\ NaNH_2} C_6H_5CH(CN)COOC_2H_5$$

$$C_6H_5CH_2CN \xrightarrow[(2)\ C_6H_5CH_2CH_2COOC_2H_5]{(1)\ NaNH_2} C_6H_5CH_2CH_2COCH(C_6H_5)CN$$

9-Phenyl- and 9-(*p*-hydroxyphenyl)phenanthrenes have been prepared by Bradsher and Kittila (128) by the acylation of *o*-phenylphenylacetonitrile with ethyl benzoate or *p*-methoxybenzoate and cyclizing the β-ketonitriles thus formed.

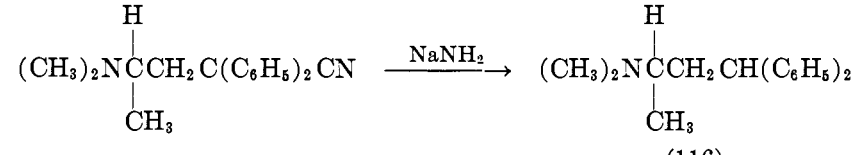


C. CLEAVAGE REACTIONS

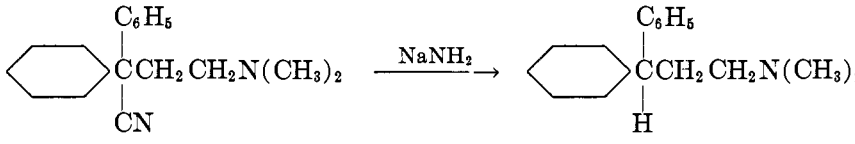
In much the same way that ketones with completely substituted α-carbon atoms are cleaved by sodium amide, trisubstituted acetonitriles are cleaved to hydrocarbons in good yields (116, 451, 453, 454, 736–738, 868). The following general equation indicates the overall reaction. Apparently one of the radicals

$$RR'R''CCN + 2NaNH_2 \xrightarrow[\text{or xylene}]{\text{refluxing toluene}} Na_2NCN + RR'R''CH + NH_3$$

R, R′, or R″ must be aromatic or heterocyclic, while the other two may be alkyl, aryl, heterocyclic, or dialkylaminoalkyl. Three examples follow.



(116)



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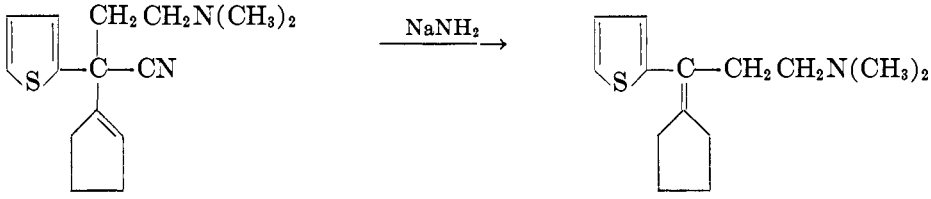


(453)

D. ALDOL-TYPE CONDENSATIONS

Phenylacetonitrile and a number of its nuclear-substituted derivatives have been condensed with a variety of symmetrical and unsymmetrical ketones in aldol-type reactions (165–167, 734, 870) to give trisubstituted acrylonitriles. Thus, the reaction of benzophenone with phenylacetonitrile (870) gives a 50–60 per cent yield of α,β,β-triphenylacrylonitrile. However, when phenylaceto-

$$RCH_2CN + R'COR'' \xrightarrow{NaNH_2} H_2O + R'R''C{=}CRCN$$

R and R′ = C_6H_5 or substituted C_6H_5; R″ = alkyl, C_6H_5, or substituted C_6H_5.

nitrile is condensed with an unsymmetrical ketone such as *p*-methoxybenzophenone (165) or propiophenone (734), a mixture of the isomeric *cis*- and *trans*-trisubstituted acrylonitriles is often obtained.

Carbocyclic ketones have also been condensed with nitriles. Thus, (2-allylcyclohexylidene)phenylacetonitrile has been prepared (880) in 28 per cent yield by the reaction of phenylacetonitrile, 2-allylcyclohexanone, and sodium amide.

When a mixture of phenylacetonitrile, sodium amide, and ethyl ether is refluxed (730), the nitrile is self-condensed and a 79 per cent yield of α,γ-diphenyl-β-iminobutyronitrile (I) is obtained. The course of this reaction is represented below. If the reaction is performed at the reflux temperature of di-*n*-butyl ether,

$$2C_6H_5CH_2CN \xrightarrow{NaNH_2,\ (C_2H_5)_2O} C_6H_5CH_2C(=NH)CH(C_6H_5)CN$$

I

$$C_6H_5CH_2CN + NaNH_2 \longrightarrow NH_3 + (C_6H_5CHCN)^-Na^+$$

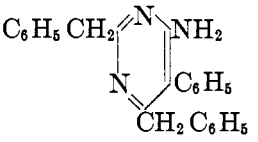
II

$$II + C_6H_5CH_2CN \longrightarrow (C_6H_5CH_2C(=N)CHC_6H_5CN)^-Na^+ \xrightarrow{H_2O} I$$

III

6-amino-2,4-dibenzyl-5-phenylpyrimidine (IV) is obtained in 89 per cent yield. Compound IV is no doubt formed from the condensation of III with

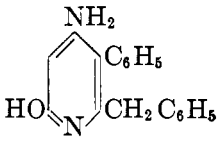
$$3C_6H_5CH_2CN \xrightarrow{NaNH_2}$$



IV

phenylacetonitrile. As an extension of this last reaction several β-acylimino-butyronitriles have been cyclized to 4-amino-2-hydroxypyridine derivatives. Thus, 4-amino-6-benzyl-2-hydroxy-5-phenylpyridine (VI) is obtained in 86 per cent yield from V, the *N*-acetyl derivative of I.

$$C_6H_5CH_2C(=NCOCH_3)CH(C_6H_5)CN \xrightarrow[(3)\ \text{tautomerization}]{(1)\ \text{cyclization by } NaNH_2;\ (2)\ H_2O}$$



V VI

A patent has been issued (666) for the preparation of β-amino-β-*n*(or iso)-propylglutaronitrile by the interaction of *n*(or iso)-butyronitrile with acetonitrile in the presence of sodium amide. The following scheme indicates a possible course for the formation of these dinitriles, using *n*-butyronitrile as an example.

$$n\text{-}C_3H_7CN + CH_3CN \xrightarrow{NaNH_2} n\text{-}C_3H_7C(=NH)CH_2CN$$

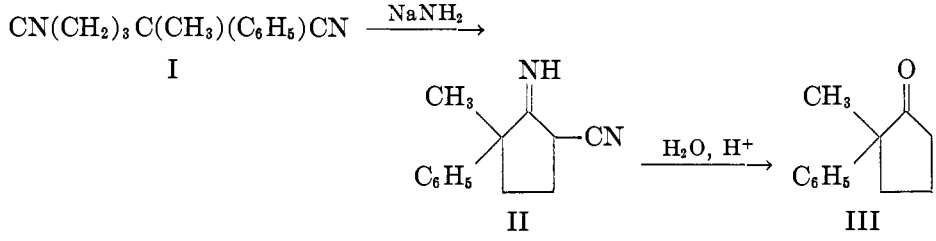
VII

$$VII + CH_3CN \xrightarrow{NaNH_2} n\text{-}C_3H_7C(NH_2)(CH_2CN)_2$$

A number of substituted benzonitriles have been condensed with the anion of acetonitrile (266). Thus, *p*-ethylbenzonitrile reacts with acetonitrile in the presence of sodium amide to give β-(*p*-ethylphenyl)-β-iminopropionitrile.

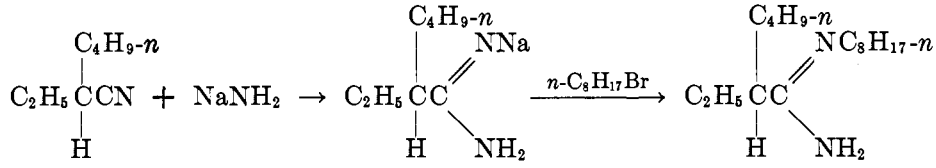
E. CYCLIZATION OF DINITRILES

Several new examples (17, 275, 428, 430, 432, 649, 656, 718) have been published in which the Thorpe–Ziegler method has been used to cyclize aliphatic dinitriles to β-iminonitriles, which may then be hydrolyzed to cycloalkanones. Thus, Newman and Closson (649) have cyclized α-methyl-α-phenyladiponitrile (I) in 85 per cent yield to 1-cyano-2-imino-3-methyl-3-phenylcyclopentane (II), which was hydrolyzed to 2-methyl-2-phenylcyclopentanone (III) in 86 per cent yield.

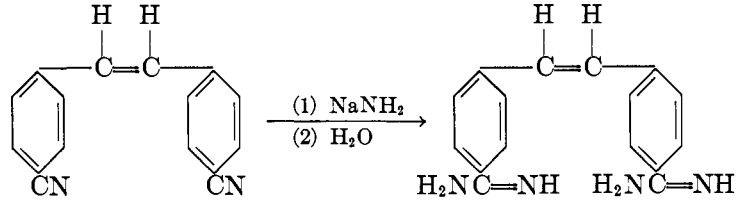


F. SYNTHESIS OF AMIDINES

Newberry and Webster (643) have prepared a number of amidines by the reaction of aliphatic nitriles with sodium amide. These amidines exist in the reaction mixtures as their sodium derivatives, which may be hydrolyzed to give the free amidine, or alkylated and acylated to give amidines which have substituents on the imino nitrogen atom.

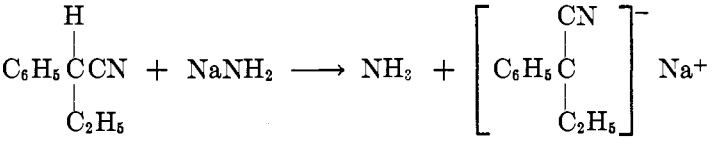


Four patents (283, 284, 589, 590) have been issued for the preparation of diamidines. The preparation of 4,4′-diamidinostilbene is typical of these syntheses (283, 590).

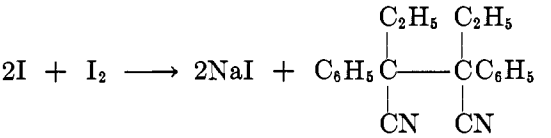


G. OTHER REACTIONS OF NITRILES

Niederl and Ziering (660) have dimerized ethylphenylacetonitrile and ethylpiperonylacetonitrile by treating their sodium derivatives with iodine and have obtained the corresponding substituted hexanes in 25 per cent yield.

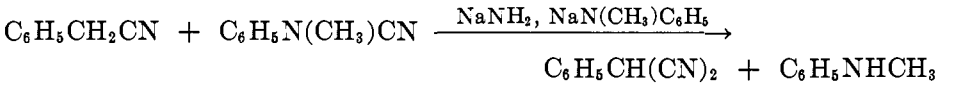


I



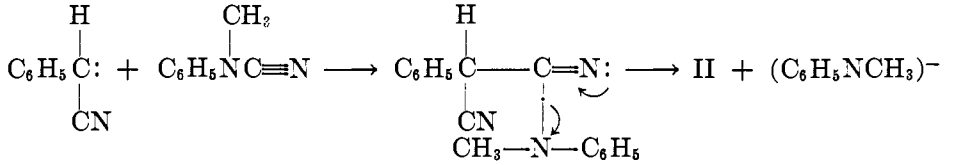
The epoxide ring of cyclohexene oxide has been opened (622) by the sodium derivatives of several nitriles to give the corresponding *trans*-2-cyanoalkylcyclohexanols. Thus, the reaction of this epoxide with sodiopropionitrile gives *trans*-2-(α-cyanoethyl)cyclohexanol.

Jungmann (470) has reported that phenylacetonitrile reacts with *N*-cyano-*N*-methylaniline in the presence of a mixture of sodium amide and sodio-*N*-methylaniline to give phenylmalononitrile (80 per cent). It is possible that this



II

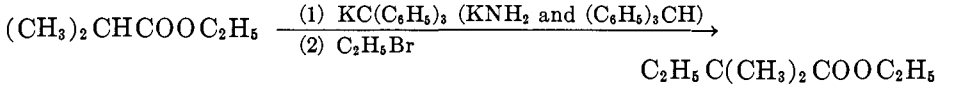
reaction involves the addition of the anion of phenylacetonitrile to the nitrile group of *N*-cyano-*N*-methylaniline, followed by the elimination of the anion of *N*-methylaniline.



XII. ESTERS

A. ALKYLATIONS

Several esters (32, 71, 74, 423, 551, 585) have been alkylated via their lithium, sodium, or potassium enolates.



(53%) (551)

$$C_6H_5CH(CN)COOC_2H_5 \xrightarrow[(2)\ ClCH_2CH_2CN]{(1)\ NaNH_2} C_6H_5C(CN)(COOC_2H_5)CH_2CH_2CN$$

(74)

$$C_6H_5CH{=}CHCH_2COOC_2H_5 \xrightarrow[(2)\ CH_3I]{(1)\ LiNH_2} C_6H_5CH{=}CHC(CH_3)_2CONH_2$$

(32)

$$C_6H_5\underset{\displaystyle OCOC_2H_5}{\overset{|}{C}}{=}CHC_6H_5 \xrightarrow[(2)\ ClCH_2CH_2N(C_2H_5)_2]{(1)\ NaNH_2} C_6H_5COCH(C_6H_5)CH_2CH_2N(C_2H_5)_2$$

(585)

In this last reaction the product probably is formed in the following way. The enol propionate of desoxybenzoin is in equilibrium with its keto form, which is alkylated to give an α-substituted β-diketone. This is then cleaved in the strongly basic reaction medium.

McElvain and Burket (595) have alkylated a number of monosubstituted malonic esters with ethyl α-chloroethyl ether to give alkyl-1-ethoxyethylmalonic esters which were condensed with urea to give barbituric acids.

Cope and Hardy (227) have prepared several Δ^1-alkenylmalonic esters by isomerizing the isomeric alkylidene compounds with sodium amide in liquid ammonia. By adding alkylating agents to the reaction mixtures, ethyl alkyl-Δ^1-alkenylmalonates may be obtained (221, 224, 225, 228, 229, 410). This latter type of reaction has also been used to prepare esters of alkyl-Δ^1-alkenylcyanoacetic acid (226).

$$(CH_3)_2C{=}C(COOC_2H_5)_2 \xrightarrow{NaNH_2} \left[CH_2{=}\underset{\displaystyle CH_3}{\overset{|}{C}}C(COOC_2H_5)_2\right]^- Na^+$$

Ethyl isopropylidenemalonate I

I —HCl→ $CH_2{=}\underset{\displaystyle CH_3}{\overset{|}{C}}CH(COOC_2H_5)_2$

Ethyl isopropenylmalonate (227)

I —$(CH_3)_2SO_4$→ $CH_2{=}\underset{\displaystyle CH_3}{\overset{|}{C}}C(CH_3)(COOC_2H_5)_2$

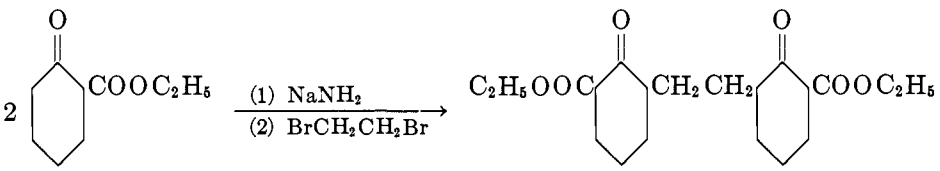
Ethyl isopropenylmethylmalonate (88%) (224)

The sodium derivatives of a number of β-ketoesters have been alkylated (153, 362, 725). Thus, ethyl acetoacetate and two of its α-substituted derivatives have been alkylated with butyl halides (725).

$$CH_3COCHRCOOC_2H_5 \xrightarrow[(2)\ R'I]{(1)\ NaNH_2} CH_3COCRR'COOC_2H_5$$

R	R'I	YIELD OF PRODUCT
		per cent
H	*iso*-C_4H_9	39
H	*sec*-C_4H_9	45
iso-C_4H_9	*n*-C_4H_9	66
sec-C_4H_9	*sec*-C_4H_9	13

The anion of ethyl 2-methylcyclopentanone-2-carboxylate has been treated with methyl iodide (153) to give ethyl 2,5-dimethylcyclopentanone-2-carboxylate. Ethylene bromide (1 mole) condenses with the anion of 2-carbethoxycyclohexanone (2 moles) (362).



B. ACYLATION OF ESTERS WITH ESTERS AND ACID CHLORIDES

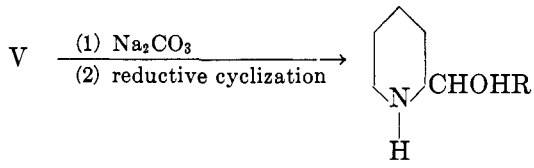
Many carbinols of the type RR'CHOH, where R is a quinoline or substituted quinoline radical and R' is the 2-piperidyl radical, have been prepared and evaluated as antimalarial drugs (10, 141–146, 457, 597, 719, 747, 769, 772, 888).

In these syntheses an ester–ester condensation is effected between a carbethoxyquinoline (I) and ethyl ε-benzamidocaproate (II) to give a substituted β-ketoester, which is then converted to the carbinol by the series of reactions shown below. If R is the 8-chloro-2-phenyl-4-quinolyl radical, the overall yield of final product, (8-chloro-2-phenyl-4-quinolyl)-2-piperidylcarbinol (VI), is 22 per cent (145).

$$\underset{\text{I}}{RCOOC_2H_5} + \underset{\text{II}}{C_2H_5OOC(CH_2)_5NHCOC_6H_5} \xrightarrow{NaNH_2}$$

$$RCOCH(CH_2)_4NHCOC_6H_5$$
$$|$$
$$COOC_2H_5$$
$$\text{III}$$

$$\text{III} \xrightarrow{HBr,\ H_2O} \underset{\text{IV}}{RCO(CH_2)_5NH_2\cdot HBr} \xrightarrow{Br_2} \underset{\text{V}}{RCOCHBr(CH_2)_4NH_2\cdot HBr}$$



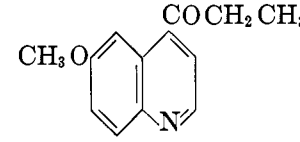
VI

A large number of β-ketoesters have been prepared by the acylation of simple esters with aliphatic (779), aromatic (779), and heterocyclic esters (231, 508, 509, 592, 779), and some of these β-ketoesters have been cleaved to ketones. Attempts to acylate phenoxyacetic esters and α-phenoxypropionic esters with esters have not met with much success (628, 629).

$$CH_3COOCH(CH_3)_2 + C_6H_5COOC_6H_5 \xrightarrow{NaNH_2} C_6H_5OH + C_6H_5COCH_2COOCH(CH_3)_2$$
(60%) (779)

$$C_6H_5CH_2COOC_2H_5 + CH_3COOC_6H_5 \xrightarrow{NaNH_2} C_6H_5OH + CH_3COCH(C_6H_5)COOC_2H_5$$
(51%) (779)

$$CH_3CH_2COOC_2H_5 \xrightarrow[(3)\ 25\%\ H_2SO_4]{(1)\ NaNH_2;\ (2)\ \text{ethyl quininate}}$$



(75%) (231)

Several esters have been acylated with acid chlorides to give β-ketoesters (254, 551, 900).

$$(CH_3)_2CHCOOC_2H_5 + C_6H_5COCl \xrightarrow[[KNH_2 \text{ and } (C_6H_5)_3CH]]{KC(C_6H_5)_3} KCl + C_6H_5COC(CH_3)_2COOC_2H_5$$
(55%) (551)

$$(C_6H_5)_2CHCOOC_2H_5 + C_6H_5COCl \xrightarrow{KNH_2} KCl + C_6H_5COC(C_6H_5)_2COOC_2H_5$$
(42%) (900)

$$(C_6H_5)_2CHCOOC_2H_5 + (C_6H_5)_2CHCOCl \xrightarrow{KNH_2} KCl + (C_6H_5)_2CHCOC(C_6H_5)_2COOC_2H_5$$
(254)

C. CARBONATION AND CARBETHOXYLATION OF ESTERS

The sodium derivatives of ethyl phenylacetate and ethyl α-phenyl-*n*-butyrate have been carbethoxylated with diethyl carbonate to give diethyl phenylmalo-

nate (64 per cent) and diethyl phenylethylmalonate (40 per cent), respectively (866).

A detailed study has been made to determine the extents to which α-hydrogen and carbonyl attack occur when esters are treated with sodium amide (386). The degree of α-hydrogen attack was determined by carbonating the reaction mixtures to give the sodium salts of the corresponding malonic acid half-esters, which were acidified and esterified with diazomethane. Which of these reactions occurs predominantly appears to depend on the acidity of the α-hydrogen atoms

$$\mathrm{RCH_2COOR' + NaNH_2} \begin{cases} \xrightarrow{\text{carbonyl attack}} \mathrm{RCH_2CONH_2 + NaOR'} \\ \xrightarrow{\alpha\text{-hydrogen attack}} \underset{\mathbf{I}}{\mathrm{Na^+(RCHCOOR')^-}} + \mathrm{NH_3} \end{cases}$$

$$\mathbf{I} \xrightarrow[(3)\ \mathrm{CH_2N_2}]{(1)\ \mathrm{CO_2},\ (2)\ \mathrm{H^+}} \mathrm{RCH(COOCH_3)(COOR')}$$

of the esters and the size of the group R'. Thus, ethyl phenylacetate, *tert*-butyl acetate, and ethyl acetate are converted to the corresponding mixed malonic esters in yields of 74, 60, and 30 per cent, respectively, while ethyl isobutyrate gives a 72 per cent yield of isobutyramide.

D. SELF-CONDENSATION OF ESTERS

A large number of esters have been self-condensed by means of lithium, sodium, and potassium amide (370, 628, 629, 779, 781). Sodium amide has usually been found to be superior to lithium amide as the condensing agent.

$$\mathrm{2C_2H_5OCH_2COOC_3H_7\text{-}\textit{i}} \xrightarrow{\mathrm{NaNH_2}}$$

$$\underset{(35\%)(628)}{\mathrm{C_2H_5OCH_2COCH(OC_2H_5)COOC_3H_7\text{-}\textit{i}}} + \underset{(35\%)(628)}{\mathrm{C_2H_5OCH_2CONH_2}} + \textit{i}\text{-}\mathrm{C_3H_7OH}$$

$$\mathrm{2C_6H_5CH_2COOC_2H_5} \xrightarrow{\mathrm{KNH_2}}$$

$$\underset{(77\%)(781)}{\mathrm{C_6H_5CH_2COCH(C_6H_5)COOC_2H_5}} + \mathrm{C_2H_5OH}$$

$$\mathrm{2CH_3COOC_3H_7\text{-}\textit{n}} \begin{cases} \xrightarrow[(60\%)(779)]{\mathrm{NaNH_2}} \\ \xrightarrow[(30\%)(370)]{\mathrm{LiNH_2}} \end{cases} \mathrm{CH_3COCH_2COOC_3H_7\text{-}\textit{n}} + \textit{n}\text{-}\mathrm{C_3H_7OH}$$

Hamell and Levine (370) have studied the self-condensations of esters with lithium amide and a series of *N*,*N*-disubstituted lithium amides, which were prepared from the secondary amines and phenyllithium. They have found that, depending on the size and the strength of the condensing base, an ester may be self-condensed (α-hydrogen attack) and/or converted to its *N*,*N*-disubstituted

amide (carbonyl attack). While ethyl propionate is converted to the β-ketoester, ethyl α-propionylpropionate, in 21 per cent yield when treated with the strong base lithium diethylamide, it gives only a trace of β-ketoester and a 57 per cent yield of *N*-methyl-*N*-phenylpropionamide when treated with the considerably

$$CH_3CH_2COOC_2H_5 \xrightarrow{LiN(C_2H_5)_2} \underset{I}{CH_3CH_2COCH(CH_3)COOC_2H_5} + C_2H_5OH \quad (21\%)$$

$$CH_3CH_2COOC_2H_5 \xrightarrow{LiN(CH_3)C_6H_5} \underset{(\text{trace})}{I} + \underset{(57\%)}{CH_3CH_2CON(CH_3)C_6H_5} + C_2H_5OH$$

weaker base, the lithium derivative of *N*-methylaniline. Furthermore, while ethyl isobutyrate is converted to isobutyramide in 72 per cent yield when treated with sodium amide (386), its reaction with lithium diisopropylamide gives the difficultly obtainable ethyl α-isobutyrylisobutyrate in 47 per cent yield in a 15-min. reaction time.

$$2(CH_3)_2CHCOOC_2H_5 \xrightarrow{LiN(C_3H_7\text{-}i)_2} \underset{(47\%)(370)}{(CH_3)_2CHCOC(CH_3)_2COOC_2H_5} + C_2H_5OH$$

E. CYCLIZATION OF ESTERS

Dieckmann cyclizations of several dibasic esters have been effected by sodium amide (66, 263, 420, 640).

$$C_2H_5OOC(CH_2)_2S(CH_2)_2COOC_2H_5 \xrightarrow{NaNH_2} \underset{(640)}{\text{O=C(COOC}_2\text{H}_5\text{)CH}_2\text{CH}_2\text{S}} + C_2H_5OH$$

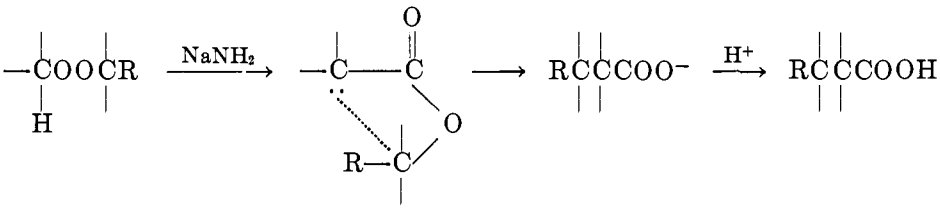
$$CH_3N(CH_2CH_2COOC_2H_5)_2 \xrightarrow{NaNH_2} \underset{(263)}{\text{O=C(COOC}_2\text{H}_5\text{)CH}_2\text{CH}_2\text{N(CH}_3\text{)}} + C_2H_5OH$$

F. REARRANGEMENT AND ELIMINATION REACTIONS

Allyl diphenylacetate (31, 535) has been rearranged to allyldiphenylacetic acid in 77 per cent yield by reaction with sodium amide (535), and allyl 9-fluorenecarboxylate has been converted to 9-allyl-9-fluorenecarboxylic acid in 97.5 per cent yield when treated with lithium amide (30, 33).

$$(C_6H_5)_2CHCOOCH_2CH{=}CH_2 \xrightarrow[(2)\ H^+]{(1)\ NaNH_2} CH_2{=}CHCH_2C(C_6H_5)_2COOH$$

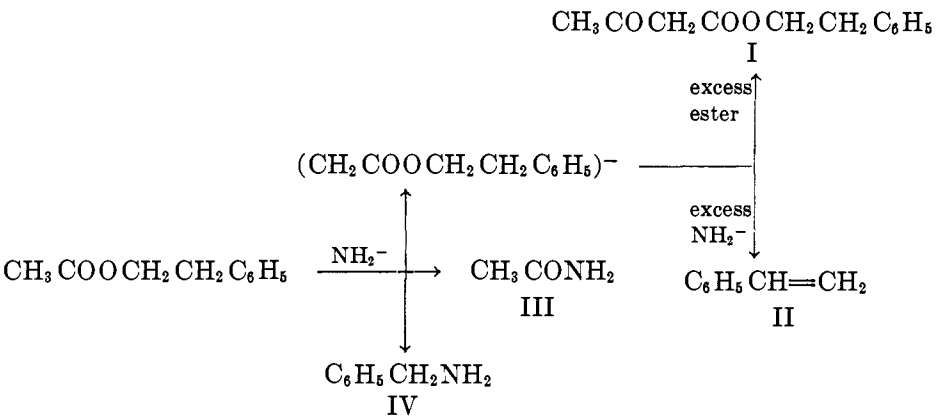
The course of these reactions, which may be written in the following generalized form, may involve the formation of the ester anion followed by an intramolecular anion attack on the α-carbon atom of the alcohol portion of the ester to give the anion of the rearranged acid. Of course, it is also possible that these rearrangements occur by a path analogous to the Claisen rearrangement of the allyl ethers of enols and phenols. If this is the case, then a transient quasi-six-



membered ring rather than the four-membered ring indicated above would be involved.

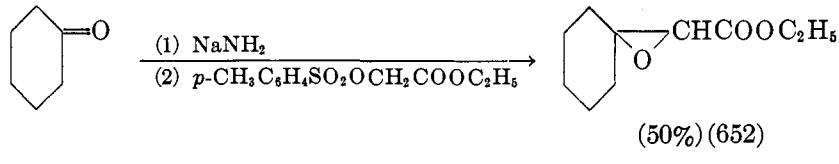
This reaction may be quite general and might be possible with esters containing a relatively acidic α-hydrogen atom in their acid portions and a radical, $-\overset{|}{\underset{|}{C}}R$, in their alcohol portions, which can form a relatively stable carbonium ion. The more acidic the α-hydrogen atom of the ester, the more readily will anion formation occur; the more stable $-\overset{|}{\underset{|}{C}}R$ is as a carbonium ion, the more readily should fission of the alkyl–oxygen bond occur and subsequent formation of the rearranged acid take place.

Hauser, Shivers, and Skell (389) have studied the reactions of esters such as β-phenylethyl acetate with sodium amide and potassium amide in liquid ammonia and have found that four types of products may be formed: a β-ketoester (I), an olefin (II), an amide (III), and an amine (IV).

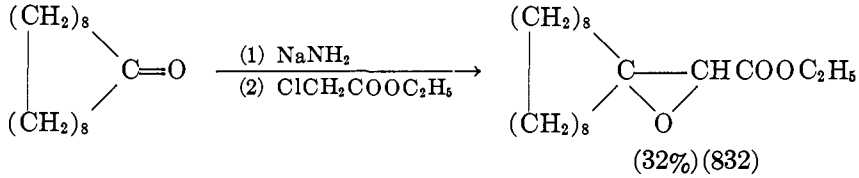


G. THE GLYCIDIC ESTER REACTION

Several glycidic esters have been prepared by condensing benzaldehyde (811), acetophenone and some of its nuclear-substituted derivatives (16, 349, 811), cyclohexanones (624, 652), dihydrocivetone (831), and β-ionone (608) with ethyl chloroacetate (16, 349, 608, 832), ethyl bromoacetate (811), ethyl α-bromopropionate (624, 811), and ethyl *p*-tosyloxyacetate (652).



(50%) (652)

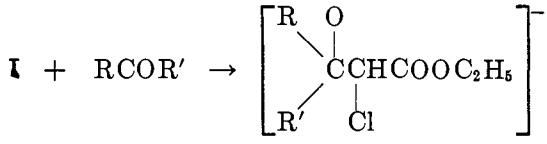


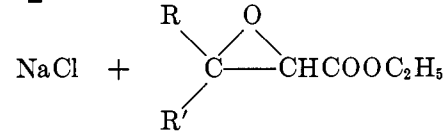
(32%) (832)

The glycidic ester condensation has been reviewed by Newman and Magerlein (654). The mechanism of this reaction appears to involve the conversion of the halo- or *p*-tosyloxyester to its anion (I) by reaction with sodium amide. The anion adds to the carbonyl carbon atom of the ketone or aldehyde and then an intramolecular nucleophilic displacement on carbon occurs to give the glycidic ester (II).

$$NaNH_2 + ClCH_2COOC_2H_5 \rightarrow NH_3 + (ClCHCOOC_2H_5)^-Na^+$$

I

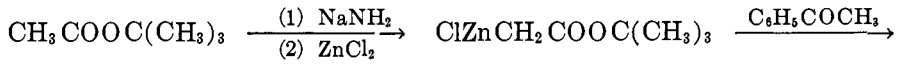




II

H. OTHER REACTIONS OF ESTERS

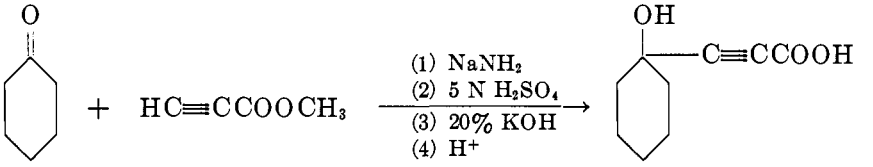
Hauser and Puterbaugh (387) have been able to effect Reformatsky-type reactions between *tert*-butyl acetate and aldehydes and ketones. The following procedures have been used:



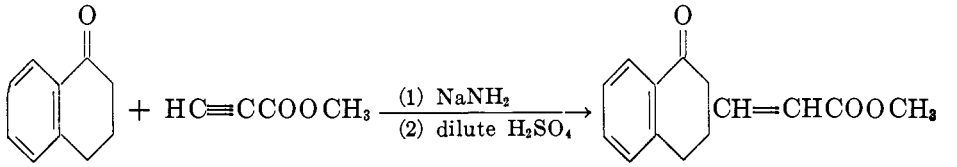
$$C_6H_5C(OH)(CH_3)COOC(CH_3)_3$$
$$\text{I}$$
$$(31\%)$$

$$CH_3COOC(CH_3)_3 \xrightarrow[(2)\ C_6H_5COCH_3]{(1)\ LiNH_2} \text{I}\ (76\%)$$

It has been found that methyl propiolate adds to the carbonyl group of cyclohexanone and 2-methylcyclohexanone in the presence of sodium amide to give the corresponding hydroxycyclohexylpropiolic acids (41). However, this ester does not add across the carbonyl groups of 1-tetralone, 6-methoxy-1-tetralone, or 1-keto-1,2,3,4-tetrahydrophenanthrene; instead, Michael reactions occur (39).



(30%)

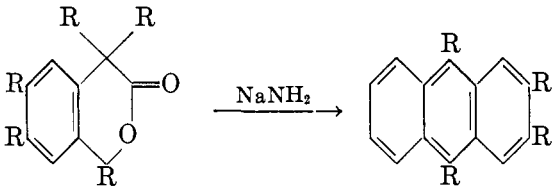


(90%)

Hoch (415) has reported that ethyl α-bromo-α-phenylacetate reacts with sodium amide to give a mixture of ethyl diphenylmaleate (45 per cent), ethyl diphenylfumarate (10 per cent), and mixed ethyl diphenylsuccinates (5 per cent).

Treatment of ethyl and *tert*-butyl cinnamates with sodium amide gives cinnamamide in yields of 76 per cent and 62 per cent, respectively, while *tert*-butyl cinnamate is converted to *N*-phenylcinnamamide in 60 per cent yield when treated with sodioaniline (393).

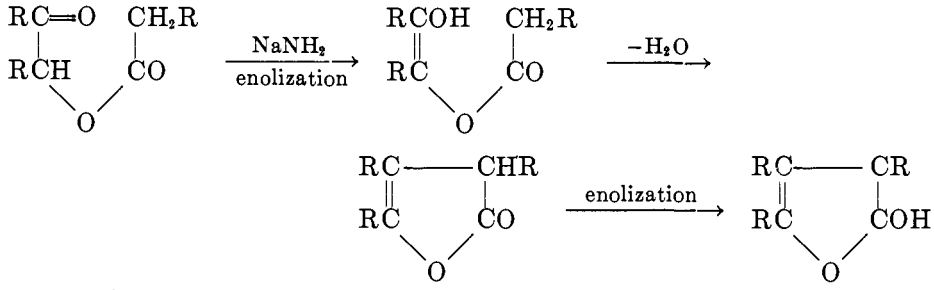
Allen and Gates (14) have obtained 2,3,9,10-tetraphenylanthracene by treating the lactone of (2-phenylhydroxymethyl-4,5-diphenyl)triphenylacetic acid with sodium amide in boiling *p*-cymene.



R = C_6H_5.

Putter and Dilthey (709) have prepared 2-hydroxy-3,4,5-triphenylfuran

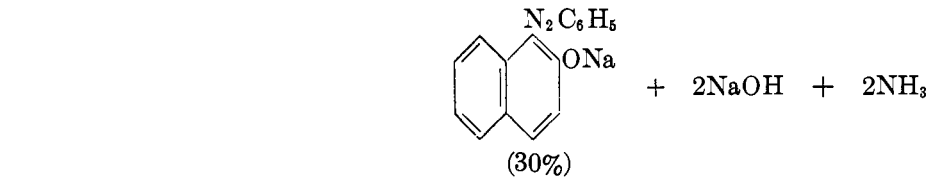
from benzoin phenylacetate and sodium amide. The reaction probably goes through the following stages:



R = C_6H_5.

XIII. Nitro Compounds

Bergstrom and Buehler (82) have effected the direct diazotization of nitrobenzene by reaction with sodium or potassium amide in liquid ammonia solution and have coupled the intermediate diazotate with β-naphthol.

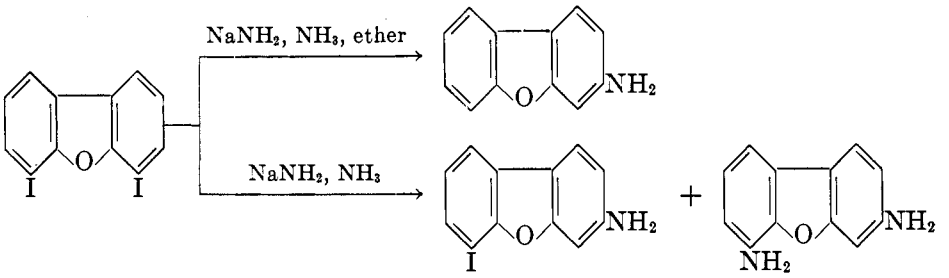


(30%)

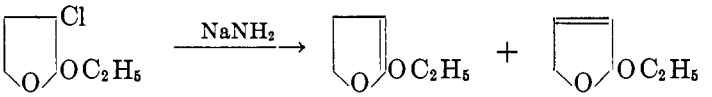
The anions of piperidine (127) and diphenylamine (85), prepared from the amines and sodium amide, have been treated with nitrobenzene to give the substitution products *p*-piperidinonitrobenzene and *p*-nitrotriphenylamine (45 per cent), respectively. Furthermore, the reaction of 1-nitronaphthalene with sodiopiperidine gave 1-nitro-4-piperidinonaphthalene. The reaction of this sodioamine with *p*-nitrotoluene gave none of the expected piperidine compound; instead the *p*-nitrotoluene was coupled to give *p*,*p*′-dinitrodibenzyl. The formation of the substitution products no doubt involves the nucleophilic attack by the amine anions at an electron-poor center of the aromatic systems, i.e., at a carbon atom which is para to the electrophilic nitro group.

XIV. Five- and Six-Membered Heterocyclic Systems Containing Oxygen

Gilman and Avakian (339) have observed that when 4,6-diiododibenzofuran is treated with sodium amide in liquid ammonia the following abnormal products are obtained. In the dibenzofuran series, the formation of abnormal products occurs when halogen atoms are located ortho to the ether linkage. Thus, while 4-bromo- and 4-iododibenzofurans give 3-aminodibenzofuran in yields of 31 and 47.5 per cent, respectively, 2-iododibenzofuran gives a 30 per cent yield of 2-aminodibenzofuran. The formation of abnormal products from the *o*-halogenated phenols and anisoles has been discussed in Section IV,E of this review.

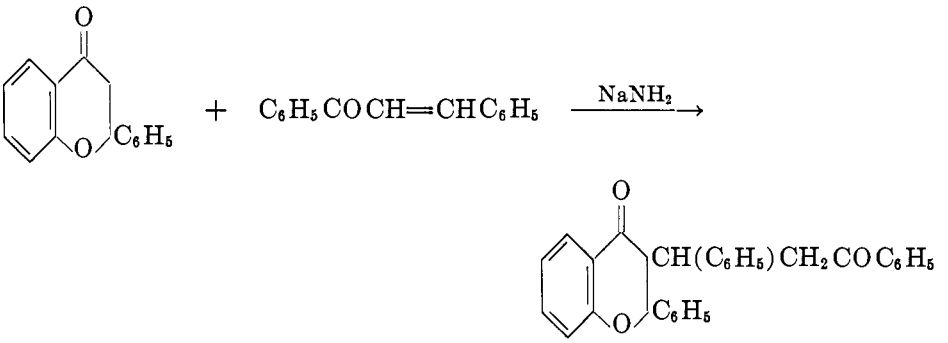


3-Chloro-2-ethoxytetrahydrofuran has been dehydrohalogenated by sodium amide to give a mixture of isomeric ethoxydihydrofurans (711).



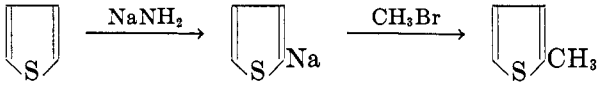
The sodium derivative of phenyl-2-furylcarbinol has been alkylated with 2-dimethylaminoethyl chloride in 45 per cent yield (704) and that of *N*-tetrahydrofurfurylaniline has been alkylated with ethyl iodide (686). Sodio-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane has been etherified in 60 per cent yield by reaction with *o*-methylbenzyl chloride (750).

A Michael condensation has been effected between 2,3-dihydro-2-phenyl-1,4-benzopyrone and benzalacetophenone (475).



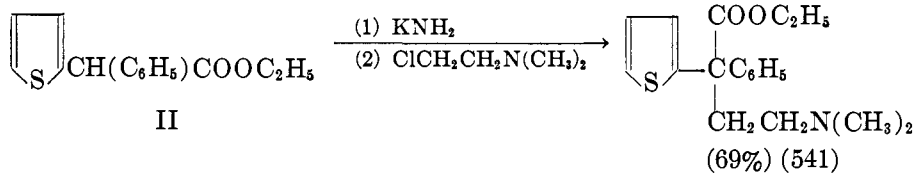
XV. Five-Membered Heterocyclic Systems Containing Sulfur

A patent has been issued (907) for the synthesis of 2-alkylthiophenes by the reaction of thiophene, sodium amide, and alkyl halides or sulfates in liquid ammonia solution.



2-Benzylthiophene has been acylated with ethyl propionate to give ethyl 2-thienylbenzyl ketone (I) and carbethoxylated with diethyl carbonate to give ethyl α-phenyl-α-(2-thienyl)acetate (II) (138), and di-2-thienylmethane has been carbethoxylated to give a 28 per cent yield of ethyl di-2-thienylacetate

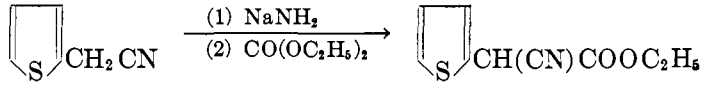
(III) (563). Compounds I, II, and III have been alkylated with a number of dialkylaminoalkyl halides (138, 541, 563).



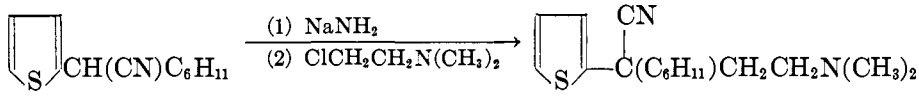
II

(69%) (541)

2-Thienylacetonitrile has been carbethoxylated in 41 per cent yield (695). This nitrile (109, 542, 843) and several of its derivatives (109, 112) have been alkylated with a variety of alkylating agents.



(41%) (695)



C_6H_{11} = cyclohexyl. (90%) (112)

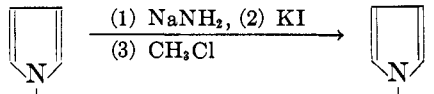
Phenyl-2-thienylcarbinol has been etherified with 2-(chloromethyl)imidazoline (249).

The reaction of 4-iodobenzothiophene with sodium amide in liquid ammonia gives the rearranged amine, 3-aminodibenzothiophene (49.6 per cent) (346).

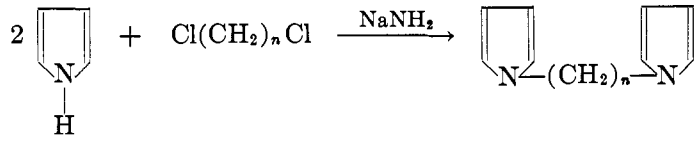
XVI. Five-Membered Heterocyclic Systems Containing Nitrogen

A. Pyrrole, Carbazole, Pyrrolidine, 2-Pyrrolidone, and Pyrazole

Sodiopyrrole has been alkylated on nitrogen by 2-diethylaminoethyl chloride (66 per cent) (278), several alkyl halides, methylene chloride (27 per cent), and 1,4-dichlorobutane (36 per cent) (766).



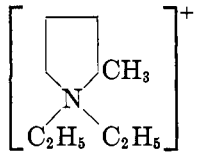
(95%)(766)



n = 1 and 4. (766)

Carbazole has been alkylated with 2-(1-pyrrolidyl)ethyl chloride to give 9-[2-(1-pyrrolidyl)ethyl]carbazole (894).

Kharasch and Fuchs (498) have found that 1,1-diethyl-2-methylpyrrolidinium chloride undergoes a Hofmann degradation when treated with sodium amide to give a mixture of 5-diethylamino-1-pentene and 4-diethylamino-1-pentene.



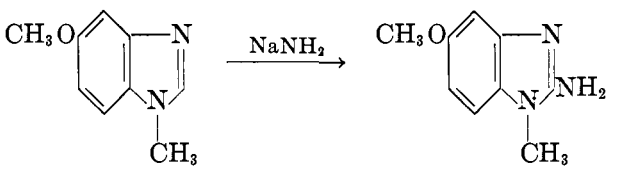
$$Cl^- \xrightarrow[150\text{–}155°C.]{NaNH_2} \begin{matrix} CH_2{=}CH(CH_2)_3N(C_2H_5)_2 \\ \text{and} \\ CH_2{=}CHCH_2CH(CH_3)N(C_2H_5)_2 \end{matrix}$$

The reactions of the sodium derivatives of 3,3,5-trimethyl- and 3,3-diethyl-5-methyl-2-pyrrolidone with a number of alkyl halides gave only *N*-alkylated products (712).

Attempts to aminate 5-chloro-3-methyl-1-phenylpyrazole with sodium amide failed (61).

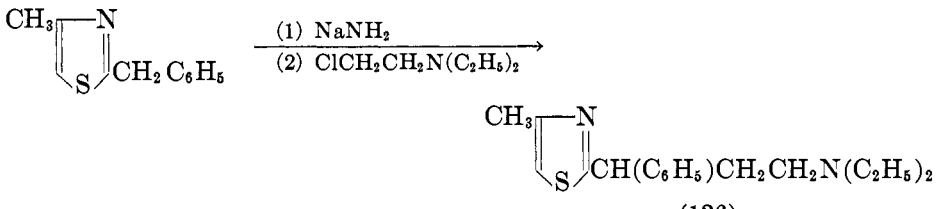
B. BENZIMIDAZOLE

5-Methoxy-1-methylbenzimidazole is converted to its 2-amino derivative (60 per cent) when treated with sodium amide in refluxing xylene (789). 2-Phenyl- and 2-*p*-methoxyphenylbenzimidazoles have been alkylated with several 2-dialkylaminoethyl halides (813).



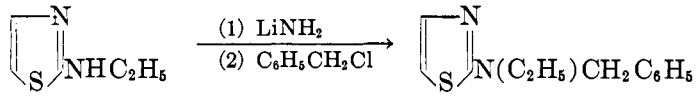
C. THIAZOLE, BENZOTHIAZOLE, THIAZOLIDINE, AND BENZOSELENAZOLE

Brody and Bogert (135) have reported unsuccessful attempts to alkylate the 2-methyl- and 2,4-dimethylthiazoles with undecylenyl, lauryl, and cetyl halides. However, the more reactive 2-benzyl-4-methyl- (136) and 2-carbethoxybenzyl-4-methylthiazoles (137) have been akylated with several 2-dialkylaminoethyl halides. Heating 4-methylthiazole with sodium amide at 150°C. for 15 hr. gives 2-amino-4-methylthiazole (675).



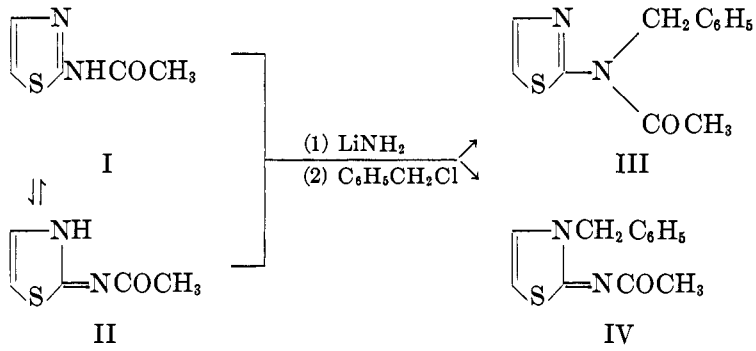
(136)

2-Aminothiazole and a number of its *N*-alkylated derivatives have been alkylated with alkyl, benzyl, and dialkylaminoalkyl halides (483, 486, 487, 490, 491).



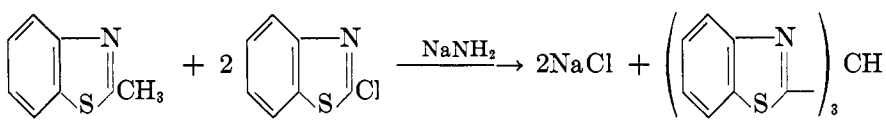
(72%) (491)

Kaye and Parris (489) found that when 2-acetamidothiazole (I) was treated with benzyl chloride, the expected compound (III) was not obtained. Instead, I reacted in its tautomeric form (II) to give 2-acetylimino-3-benzylthiazoline (IV) in 39 per cent yield.



When benzothiazole is treated with sodium amide in decalin at 140°C., 2-aminobenzothiazole and 2,2′-diaminodiphenyl disulfide are formed (677). Apparently no 2-aminobenzothiazole is formed when 2-chlorobenzothiazole is treated with potassium amide (540).

2-Methylbenzothiazole has been alkylated (235) and heterylated (492) at the methyl group. Lithium amide has been used to effect the alkylation of the secondary amino group of 2-benzylamino-6-methoxybenzothiazole with 2-diethylaminoethyl chloride in 96 per cent yield (488).



(492)

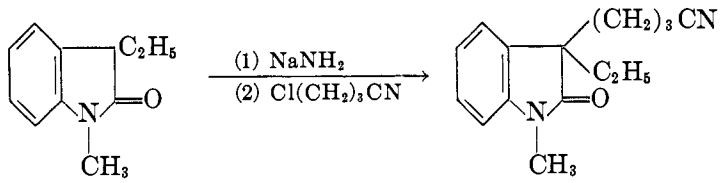
Methyl 3-chloroacetyl-4-thiazolidinecarboxylate is recovered unchanged when it is treated with sodium amide in liquid ammonia in an attempt to replace the chlorine atom by the amino group (642). When α-sodium-β-methylbenzylpenicilloate is treated with sodium amide and *p*-bromobenzyl bromide in liquid ammonia, α-sodium-β-methyl-7-(*p*-bromobenzyl)benzylpenicilloate is obtained (694).

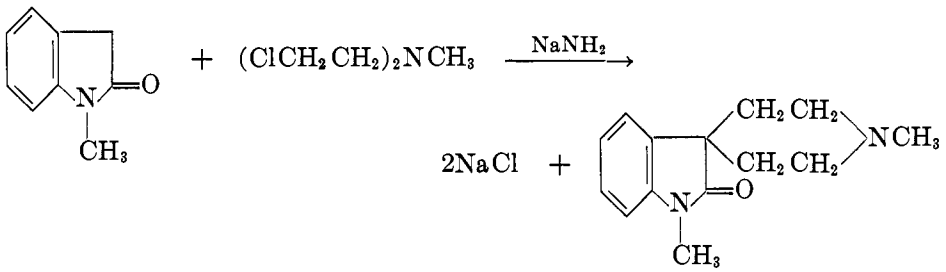
The attempted amination of benzoselenazole with sodium amide in decalin fails. Instead, a small amount of 2,2′-diaminodiphenyl diselenide is formed (668).

D. OXINDOLE AND INDOXYL

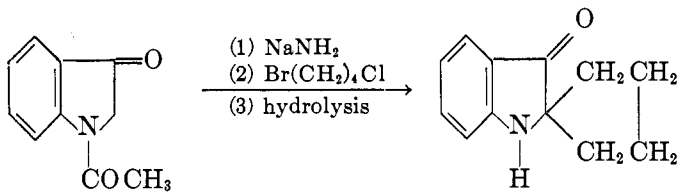
3-Ethyl-1-methyloxindole has been alkylated with β-dimethylaminoethyl chloride and γ-chlorobutyronitrile in yields of 65 per cent and 52 per cent, re-

spectively (434). 1-Methyl-, 1-methyl-5-ethoxy-, and 1-methyl-6-ethoxyindoles have been alkylated with methylbis(β-chloroethyl)amine to give piperidine derivatives (278, 523) in yields of 38 to 51 per cent.





The keto form of *N*-acetylindoxyl has been alkylated with tetramethylene chlorobromide to give 2,2-tetramethyleneindoxyl after hydrolysis (682).



XVII. Six-Membered Heterocyclic Systems Containing Nitrogen

A. PYRIDINE AND ITS DERIVATIVES

1. Amination and related reactions

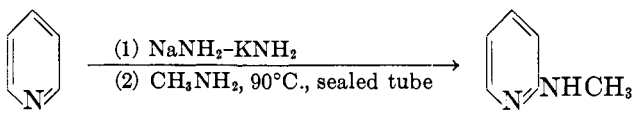
In 1914 Chichibabin (83, page 154; 84, page 463; 194, 200) discovered that 2-aminopyridine can be formed in good yields (40–50 per cent) by treating pyridine with sodium amide in a refluxing aromatic solvent such as xylene. This reaction, one of the most important in the pyridine series, has been studied intensively; the work which has been done on the amination of heterocyclic bases through 1938 has been reviewed by Leffler (539).

Yields of 2-aminopyridine as high as 80 per cent may be obtained by heating a mixture of pyridine, sodium amide, and dimethylaniline at 105–110°C. for 8–10 hr. (754; 539, page 99). It has also been obtained by treating an emulsion of sodium in hot mineral oil with ammonia and pyridine (209) and by the reaction of sodium amide with pyridine in a ball-mill reactor (786).

As extensions of the Chichibabin method the following substituted pyridines have been aminated: 2-picoline (683, 802), 2,4-lutidine (537), 3-picoline (94,

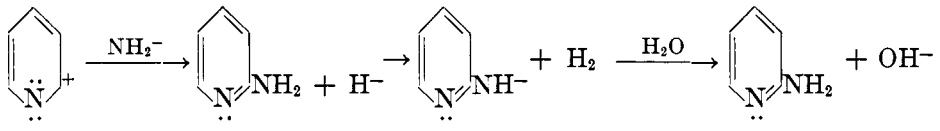
211), 3,4-dihydroxypyridine (62), nicotinamide (173), *N*-methylanabasine (471), nicotyrine (214), 4-picoline (565), 4-*n*-propylpyridine (809), and β-carboline (801). Thus, e.g., depending on reaction conditions, 3-picoline has been aminated to give a mixture of 2-amino-3-methylpyridine and 2-amino-5-methylpyridine (211) or 2,6-diamino-3-methylpyridine (94).

2-Alkylaminopyridines can be prepared in good yields by the reaction of pyridine, a primary amine, and the fused eutectic of sodium–potassium amide. This method gave a 73 per cent yield of 2-methylaminopyridine (91). Attempts to extend the reaction to the synthesis of 2-dialkylaminopyridines failed (91). Also, Hauser and Weiss (392) were unable to get substituted 2-amino-



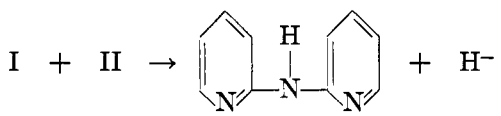
pyridines from the reactions of pyridine with sodio-*N*-methylaniline and lithio-di-*n*-butylamine.

Several workers (77, 255, 510, 906) have proposed mechanisms for the amination of pyridine. The most reasonable appears to be that suggested by Deasy (255). In this scheme, the amination is regarded as involving a nucleophilic attack by the amide ion on the electron-poor 2-position of the pyridine ring, followed by the elimination of a hydride ion. This scheme also explains the



I II

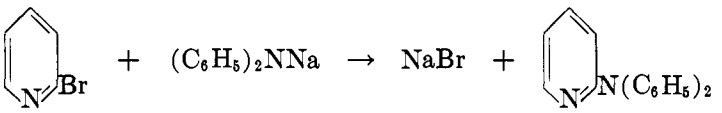
formation of the by-product, 2,2′-dipyridylamine, and why the presence in the



heterocyclic ring of meta-directing groups increases the yields of aminated products, while the presence of ortho- and para-directing groups has an adverse effect on the yields of aminated products. Thus, while quinoline is aminated to give a 53 per cent yield of 2-aminoquinoline (77), 2-carboxyquinoline gives an 81 per cent yield of 4-aminoquinoline-2-carboxylic acid (78); furthermore, while pyridine is aminated in yields as high as 80 per cent, 3-aminopyridine gives only a low yield of 2,3-diaminopyridine (517).

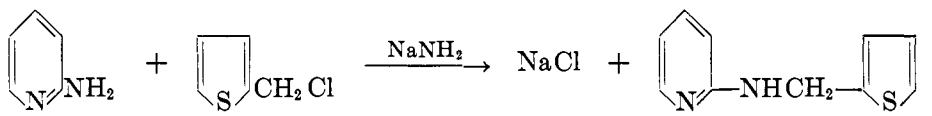
Hauser and Weiss (392) have shown that 2-bromopyridine reacts with nucleophilic reagents in much the same way that pyridine does. Thus, the reactions of 2-bromopyridine with sodium amide, sodio-*N*-methylaniline, and sodiodiphen-

ylamine give 2-aminopyridine (67 per cent), 2-methylanilinopyridine (57), and 2-diphenylaminopyridine (17 per cent), respectively.

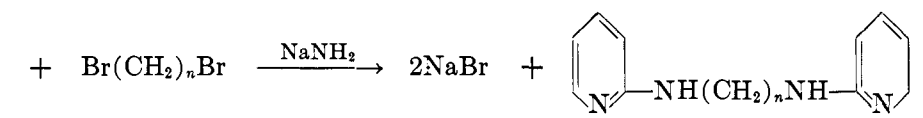


2. Alkylation and heterylation of aminated pyridines and related compounds

Many secondary amines have been prepared in good yields by condensing the lithium or sodium derivative of 2-aminopyridine with a variety of halides such as alkyl halides (775, 825), polymethylene dihalides (774), dialkylaminoalkyl halides (175, 262, 447, 484, 530, 543, 559, 878), benzyl halides (97, 485), thenyl halides (484, 531), 3-thianaphthenylmethyl chloride (113), haloacetals (482), haloalcohols (898), 2-chlorothiazole (259), and 2-chloropyrimidine (259). The following examples are typical.



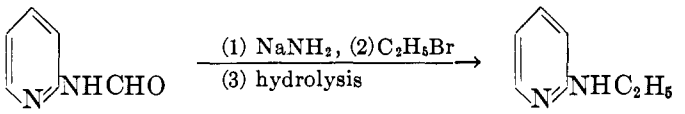
I (59%) (531)



(n = 2, 14%; n = 6, 80%) (774)

Sharp (775) has observed that when 2-aminopyridine is alkylated with decyl iodide, a number of its higher homologs, and benzyl bromide, small amounts of the isomeric 1-alkyl-2-pyridonimines are formed in addition to the expected major products, the 2-alkylaminopyridines.

Blicke and Tsao (115) have found that 2-alkylaminopyridines are formed in fair to good yields by hydrolyzing the disubstituted formamides obtained by alkylating 2-formylaminopyridine.

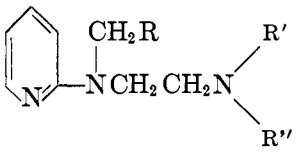


(81%)

Sodio-6-amino-2-methylpyridine has been alkylated with dimethyl sulfate to give 6-dimethylamino-2-methylpyridine (285).

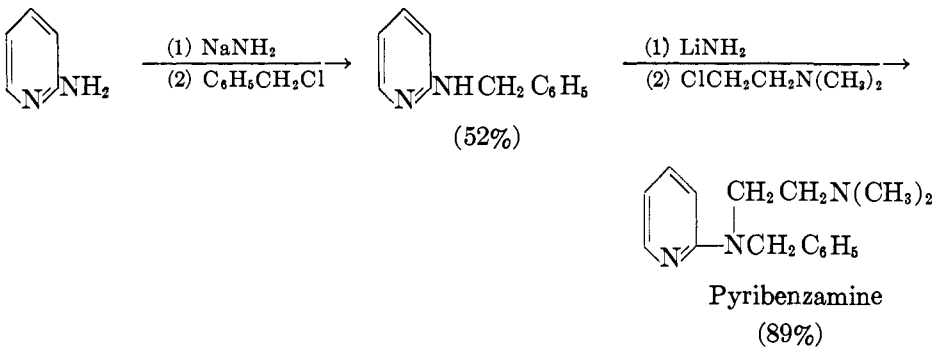
Many of the secondary amines prepared as described above, as well as others, have been alkylated and heterylated with a variety of halides to give tertiary amines (97, 113, 174, 175, 180, 212, 262, 327, 355, 367, 395, 425, 437, 438, 447, 483, 486, 490, 530, 532, 543, 559, 803, 816, 838, 845, 857, 865) of the following

structure:



R = alkyl, aryl, or heterocyclic; R′ and R″ = alkyl or part of a ring as in piperidine.

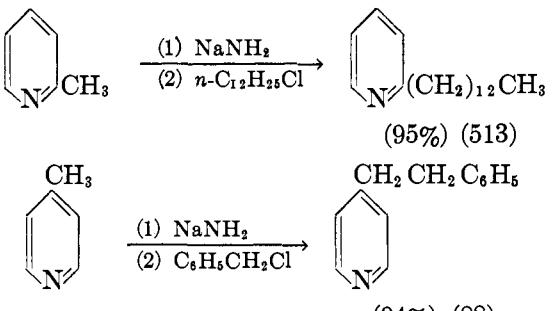
A number of these tertiary amines have found wide application in the treatment of histamine allergies. A synthesis of the widely used antihistaminic, Pyribenzamine, follows (447).



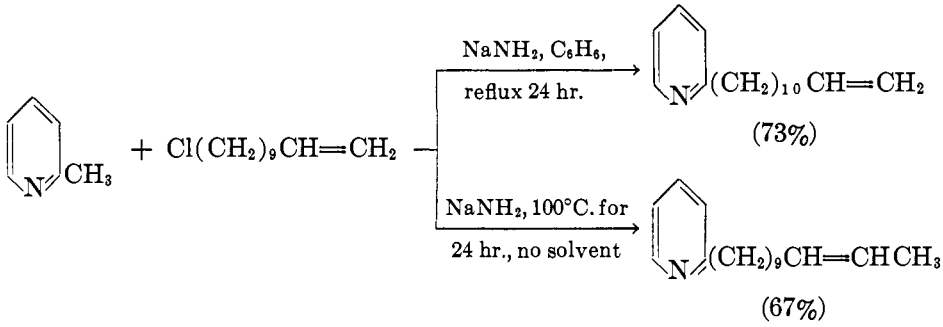
4-Benzylaminopyridine and its 2-methyl and 2,6-dimethyl derivatives have been alkylated in good yields with a number of 2-dialkylaminoethyl halides (479, 480).

3. Synthesis and reactions of alkyl-, aralkyl-, and heteroalkylpyridines

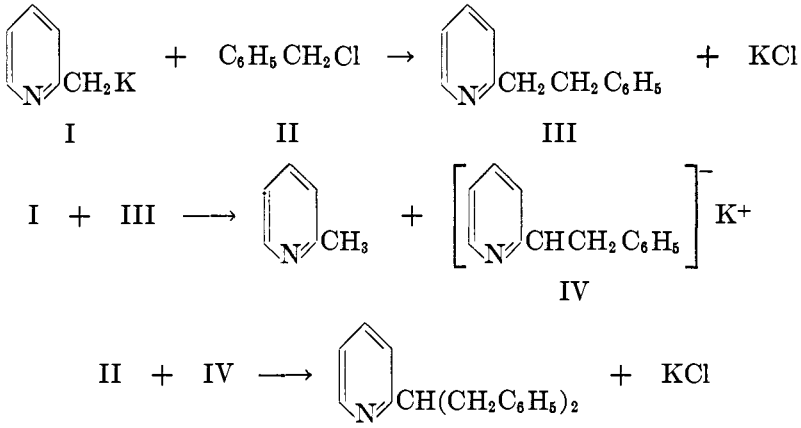
The alkylations of 2- and 4-picoline, which have been studied by Chichibabin and coworkers (84, page 467; 328), have received much attention in recent years. Thus, 2-picoline (50, 88, 134, 139, 196, 197, 513, 571, 572, 755, 822, 823, 881) and 4-picoline (50, 88, 139, 196, 197, 210, 755, 772) have been treated with alkyl halides (50, 88, 139, 196, 513, 571, 572, 755, 777), olefinic halides (134), dialkylaminoalkyl halides (196, 197, 823), alicyclic halides (210, 822), 2-thenyl halides (822), haloethers (197), and haloacetals (881). Two typical examples follow.



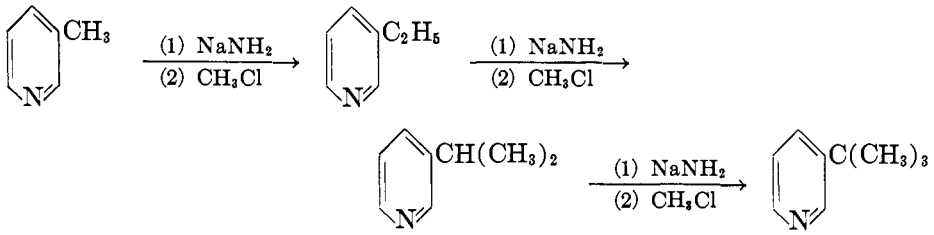
A few of the alkylation studies have given especially interesting results. Brody and Bogert (134) have alkylated 2-picoline with 11-chloro-1-undecene, and, depending on reaction conditions, have obtained one of the isomeric 2-alkylpyridines indicated in the following scheme:



Chichibabin (195, 196) found that significant amounts of dialkylated products are formed when 2-picolylsodium is treated with alkyl and aralkyl halides. In a reinvestigation of this work (88), it has been possible to obtain high yields of monosubstitution products by adding the alkylating agents rapidly to a liquid ammonia solution of the potassium derivatives of 2-picoline, 4-picoline, and quinaldine. Thus, 2-picoline and 4-picoline have been monobenzylated by benzyl chloride in yields of 68 and 94 per cent, respectively. The rapid addition of the alkylating agent favors the first reaction shown below and minimizes the extents to which the second and third reactions occur.

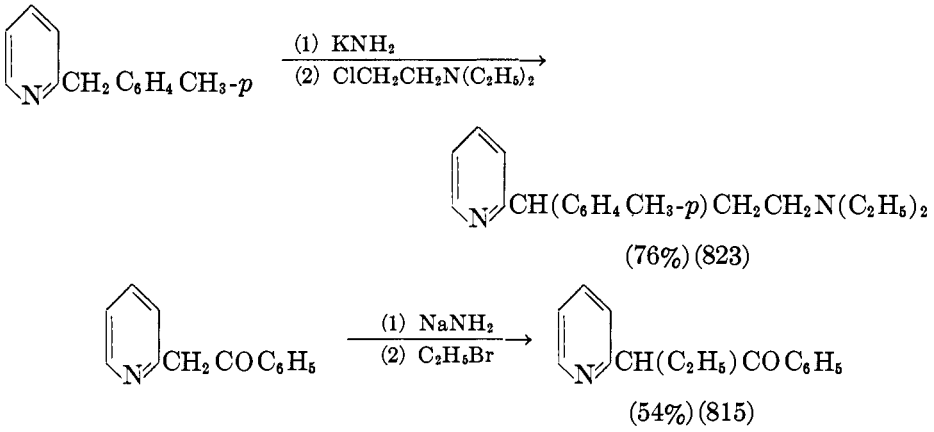


Brown and Murphey (139) have published an extremely significant paper concerning the alkylation of the isomeric picolines. These workers are the first to report the successful alkylation of 3-alkylpyridines. Thus, they have been able to prepare 3-ethyl-, 3-isopropyl-, and 3-*tert*-butylpyridine in yields of 54, 51, and 23 per cent, respectively, by methylating 3-sodioalkylpyridines in liquid ammonia solution. These results indicate that the activating inductive effect of the pyridine nitrogen atom is sufficiently great to enable alkyl groups attached to the 3-position of the pyridine ring to be metalated by sodium amide.



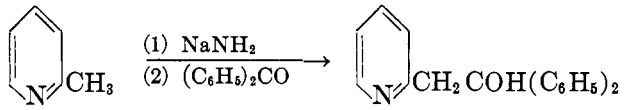
Similarly, these workers have been able to prepare the isomeric 2- and 4-ethyl-, isopropyl-, and *tert*-butylpyridines in good yields and have ethylated 2-picoline with ethyl bromide in 55 per cent yield. These results are of special interest, because Chichibabin (194) reported that 2-picoline could not be methylated with methyl iodide in the presence of sodium amide, and Bergstrom (75) reported that the ethylation of 2-picoline with ethyl bromide in the presence of potassium amide failed.

2-Benzylpyridine (819), 2-(*o*-methoxybenzyl)pyridine (680), 2-(*p*-xylyl)pyridine (823), and 2-phenacylpyridine (815) have been alkylated in good yields.



Dirstine and Bergstrom (261) have been able to phenylate 2-picoline with chlorobenzene in the presence of excess potassium amide in liquid ammonia solution to give a mixture of 2-benzylpyridine (24 per cent), 2-benzhydrylpyridine (18 per cent), and 2-tritylpyridine (18 per cent).

Chichibabin (198) has found that although 2-picolylsodium reacts with benzophenone to give a high yield of (2-picolyl)diphenylcarbinol, attempts to use aliphatic ketones in similar reactions gave low yields of products. Similarly, benzaldehyde gave benzamide and a low yield of phenyl(2-picolyl)carbinol.



Although Chichibabin (198) obtained only a low yield of 2-phenacylpyridine from the reaction of 2-picolylsodium and ethyl benzoate, yields of 57 per cent

(871) and 44 per cent (440) were obtained recently when 2-picolylpotassium was used in place of the sodium derivative. The carbethoxylation of 2-picolylpotassium with diethyl carbonate has given a 25 per cent yield of ethyl 2-pyridylacetate (871).

Weiss and Hauser (872) have found that 2-picolylsodium reacts with benzalacetophenone to give two compounds: $C_{39}H_{31}NO_2$ (A) and $C_{54}H_{43}NO_2$ (B). Compound A is formed by a Michael condensation between one molecule of 2-picoline and two of benzalacetophenone, while B is formed by Michael condensations involving one molecule of the tar base and three of the ketone. The postulated course for the formation of A follows.

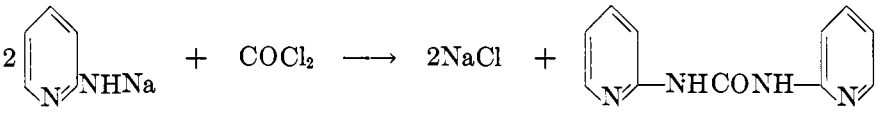
$$RCH_3 \xrightarrow[(2)\ R'CH{=}CHCOR']{(1)\ NaNH_2}$$

$$RCH_2CHR'CH_2COR' \xrightarrow[(2)\ R'CH{=}CHCOR']{(1)\ NaNH_2} \underset{\displaystyle HCCOR'}{\overset{\displaystyle R'CHCH_2COR'}{\overset{|}{\underset{|}{}}}}\\ \underset{\displaystyle HCR'CH_2R}{\overset{|}{}}\\ A$$

R = 2-C_5H_4N, i.e., 2-pyridyl; R′ = C_6H_5.

4. Other reactions of compounds containing pyridine rings

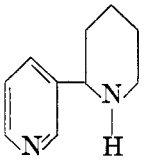
Sodio-2-aminopyridine has been treated with phosgene to give 1,3-di-2-pyridylurea, but 2-amino-5-nitropyridine fails to undergo this reaction (336).



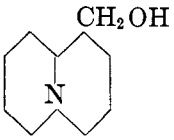
The sodium derivative of 1,3-dimethyl-2-azafluorenol has been etherified by 2-dimethylamino- and 2-diethylaminoethyl chlorides (286).

9-Chloro-1,3-dimethyl-9-phenyl-2-azafluorene has been converted to 9-amino-1,3-dimethyl-9-phenyl-2-azafluorene by reaction with potassium amide in liquid ammonia in a sealed tube. Under similar conditions, 1,3-dimethyl-9-phenyl-2,10-diazaphenanthrene has been converted to 9-amino-1,3-dimethyl-2,10-diazaphenanthrene (65).

A mixture of anabasine and lupinine may be separated by treatment with sodium amide in liquid ammonia. Under these conditions the sodium lupinate, which precipitates, may be removed by filtration and the filtrate may be concentrated to give anabasine (745).



Anabasine



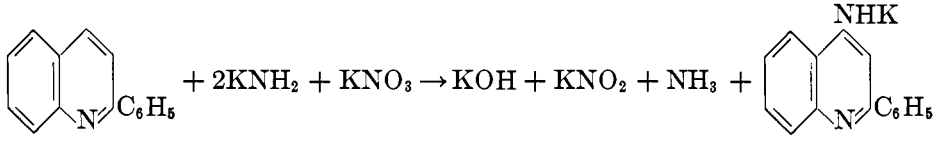
Lupinine

B. QUINOLINE, ISOQUINOLINE, AND THEIR DERIVATIVES

1. Amination and related reactions

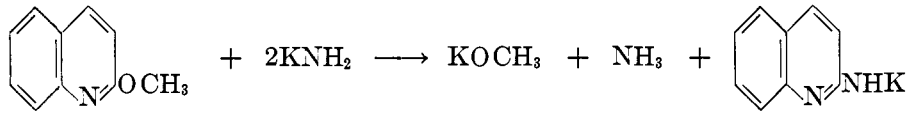
The amination of a number of quinolines (77–79, 91, 350, 351) and isoquinolines (89–91) has been studied as extensions of the earlier work of Chichibabin and his coworkers (199, 201).

In an earlier review (76; 83, page 158), Bergstrom reported that the attempted amination of quinoline with sodium amide failed. In a reinvestigation of this reaction (77) he found that quinoline, when treated with potassium amide and potassium nitrate, is aminated to give a mixture of 2-aminoquinoline (50 per cent) and 4-aminoquinoline (10 per cent). When similarly treated, 2-phenylquinoline gives a good yield of 4-amino-2-phenylquinoline (79).



Although 2-methylquinoline (quinaldine) and 4-methylquinoline (lepidine) react with sodium and potassium amides in liquid ammonia to form salts, these salts are not aminated by potassium amide even in the presence of potassium nitrate (78).

Quinoline-2-sulfonic acid and 2-methoxyquinoline are converted to 2-aminoquinoline when treated with potassium amide in liquid ammonia, but 2-hydroxy-, 8-hydroxy-, and 2-aminoquinolines are not aminated when treated with potassium amide in liquid ammonia in the presence or absence of potassium nitrate at temperatures up to 110°C. (78).



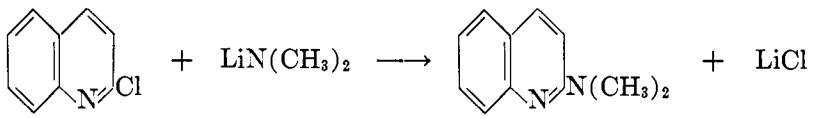
Reaction of quinaldinic and cinchoninic acids with potassium amide and potassium nitrate in liquid ammonia gave 4-aminoquinoline-2-carboxylic acid (81 per cent) and 2-aminoquinoline-4-carboxylic acid (70 per cent), respectively (78).

Although it was originally reported that the reaction of quinoline, methylamine, and the eutectic of sodium and potassium amides in excess methylamine gave one product, 2-methylaminoquinoline (91), more recent work on the course of this reaction (350, 351) has shown that a mixture of the 2-amino- and 2-methylaminoquinolines is formed.

1-Aminoisoquinoline (57 per cent), but none of the expected 1-cyclohexylaminoisoquinoline, was obtained when isoquinoline was treated with the sodium–potassium amide eutectic in boiling cyclohexylamine (91). Reaction of 3-methylisoquinoline with potassium amide and potassium nitrate in liquid ammonia gave a 70 per cent yield of 1(?)-amino-3-methylisoquinoline (89). While

the reaction of 4-bromoisoquinoline with potassium amide in liquid ammonia gave only tars, similar treatment of isoquinoline-4-carboxylic acid gave a 71 per cent yield of the potassium salt of 1-amino-4-carboxyquinoline (90).

Gilman and coworkers (340) have treated 2-chloroquinoline with lithiodimethylamine and lithioethylenimine in liquid ammonia and have obtained 2-dimethylamino- and 2-ethyleniminoquinolines in yields of 58 and 73 per cent, respectively. A similar study has been made by Hauser and Weiss (392), who have



treated 2-chloroquinoline with sodium amide, sodioaniline, and sodio-*N*-methylaniline and obtained 2-aminoquinoline (22 per cent), a mixture of 2-anilinoquinoline (20 per cent) and di-2-quinolylphenylamine (20 per cent), and 2-methylanilinoquinoline (47 per cent), respectively.

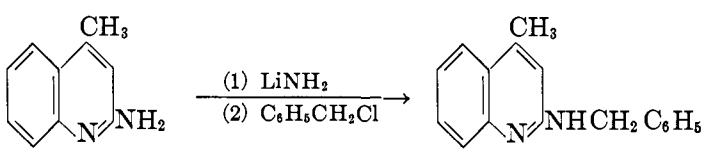
Refluxing 5,6,7,8-tetrahydroquinoline with sodium amide in refluxing dimethylaniline has given an 85 per cent yield of the 2-amino derivative (348).

2. Alkylation of aminated quinolines and related compounds

Several aminoquinolines containing an amino group in various positions of the benzene ring have been alkylated with dialkylaminoalkyl halides (22, 566, 899). Thus, the sodium derivative of 8-amino-5,6-methylenedioxyquinoline was alkylated on the amino nitrogen atom in 20 per cent yield by 3-diethylaminopropyl chloride in refluxing toluene and sodio-8-amino-6-methoxyquinoline was alkylated with the same halide in 94 per cent yield when the reaction was performed in liquid ammonia solution in a sealed tube at room temperature (22).

3-Dimethylamino-1,2,3,4-tetrahydroquinoline has been alkylated on its imino nitrogen atom by benzyl chloride and a number of nuclear-substituted benzyl chlorides (365).

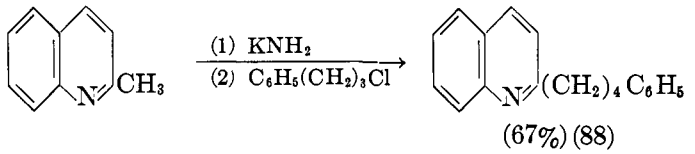
The syntheses of a number of derivatives of 2-aminolepidine have also been reported (481, 483, 484, 486, 490).



(74%) (481)

3. Alkylation, arylation, and heterylation of alkylated quinolines

The sodium and potassium derivatives of quinaldine (88, 492, 672) and lepidine (88, 197, 492) have been condensed with alkyl halides (88, 672), benzyl and nuclear-substituted benzyl halides (88), dialkylaminoalkyl halides (197), and heterocyclic halides (492).



Quinaldine and lepidine have been phenylated by chlorobenzene in the presence of excess potassium amide in liquid ammonia solution (261). Thus, from lepidine, a mixture of 4-benzylquinoline (37 per cent) and 4-benzhydrylquinoline (30 per cent) was obtained. However, attempts to phenylate 2-*n*-propyl- and 2,4-dimethylquinolines failed.

4. Acylation of alkylated quinolines and related reactions

Bergstrom and Moffat (87) have studied the Claisen acylation of the potassium derivative of the cyclic ammono ketone ether, quinaldine, with ethyl 2-furoate, ethyl benzoate, and the ethyl esters of several nuclear-substituted benzoic acids and have obtained acyl quinaldyl ketones in fair to good yields. However, the reaction failed with ethyl acetate and ethyl oxalate.

Weiss and Hauser (871) have reinvestigated this work and have also studied the acylation of lepidine. Thus, e.g., they have condensed quinaldine with phenyl acetate (17 per cent), phenyl propionate (32 per cent), ethyl isobutyrate (36 per cent), and diethyl carbonate (36 per cent); and lepidine has been acylated with ethyl benzoate (44 per cent), ethyl oxalate (60 per cent), and diethyl carbonate (14 per cent). The mechanism for these acylations is shown in the following scheme, where P represents the 2- or 4-quinolyl radical. The course of these reactions is identical with that discussed for the acylation of ketones with esters in Section VIII,A of this review.

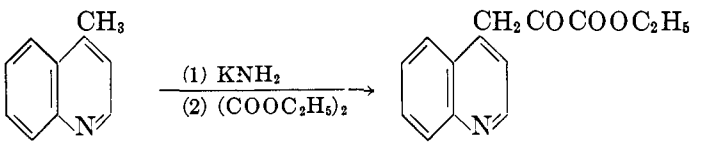
$$CH_3P + KNH_2 \longrightarrow KCH_2P + NH_3$$

$$RCOOR' + KCH_2P \longrightarrow RCOCH_2P + KOR'$$

$$RCOCH_2P \xrightarrow{KNH_2} (RCOCHP)^-K^+ + NH_3$$

$$RCOCH_2P \xrightarrow{KCH_2P} (RCOCHP)^-K^+ + CH_3P$$

Although the reaction of ethyl oxalate with potassiolepidine gave a 60 per cent yield of the expected product, ethyl 4-quinolylpyruvate (I) (871), the reaction of this ester with potassioquinaldine gave the unexpected 2-quinaldal-3-(2-quinolyl)propanoic acid (III) in 53 per cent yield (383). The analogous propanoic acid (23 per cent) was obtained from the reaction of 2-picolylpotassium and ethyl oxalate.



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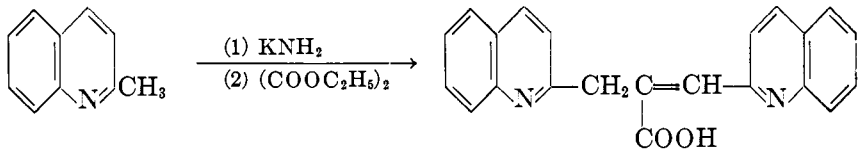
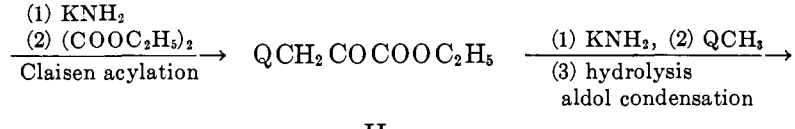
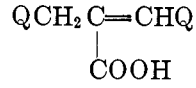


III

Compound III is probably formed by an aldol condensation between the intermediate ethyl 2-quinolylpyruvate (II) and quinaldine, QCH_3.

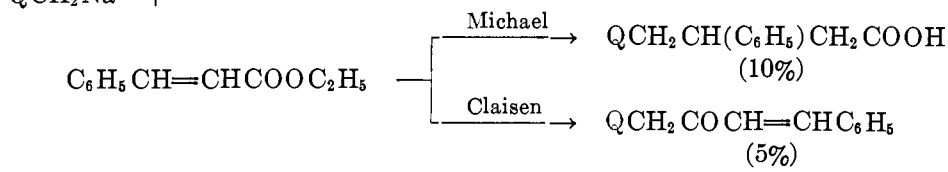


II



III

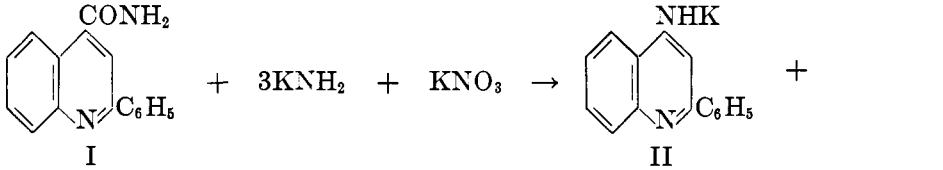
Sodioquinaldine and sodiolepidine undergo Michael reactions (872) with benzalacetophenone to give β-phenyl-γ-(2-quinolyl)butyrophenone (60 per cent) and β-phenyl-γ-(4-quinolyl)butyrophenone (27 per cent), respectively. However, sodioquinaldine reacts with ethyl cinnamate by both 1,4-addition (Michael reaction) and 1,2-addition (Claisen condensation (872)).



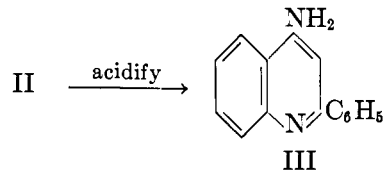
Sodioquinaldine reacts with benzophenone to give a good yield of diphenylquinaldylcarbinol (198).

5. Other reactions of compounds containing quinoline rings

White and Bergstrom (877) have studied and proposed a mechanism for the occurrence of Hofmann-type rearrangements when certain heterocyclic amides are treated with potassium amide and potassium nitrate in liquid ammonia solution. The conversion of 2-phenylquinoline-4-carboxamide (I) to 4-amino-2-phenylquinoline (III) in 90–98 per cent yield is a typical reaction.

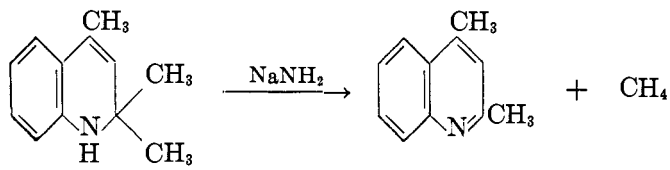


I II



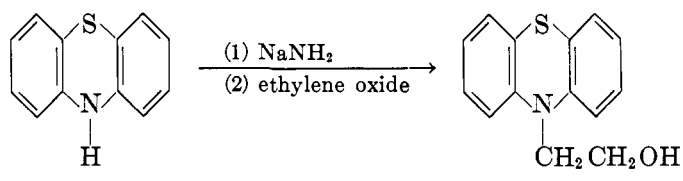
III

Craig (236) has reported that 1,2-dihydro-2,2,4-trimethylquinoline is converted to 2,4-dimethylquinoline in 86 per cent yield when treated with sodium amide.

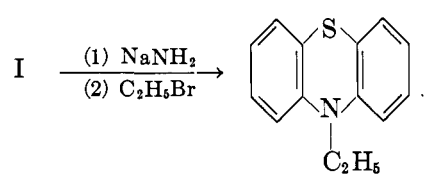


C. PHENOTHIAZINE

The sodium and/or lithium derivatives of phenothiazine have been condensed with ethyl bromide (345), benzyl chloride (345), 2-(chloromethyl)imidazoline (207, 607), ethylene oxide (251), propylene oxide (250), and a number of dialkylaminoalkyl halides (192, 250, 251, 446, 722, 804, 896). Two typical examples follow.



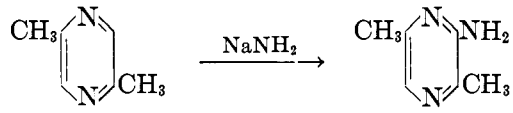
I (55%) (251)



(92–97%) (345)

D. PYRAZINE AND PYRIMIDINE

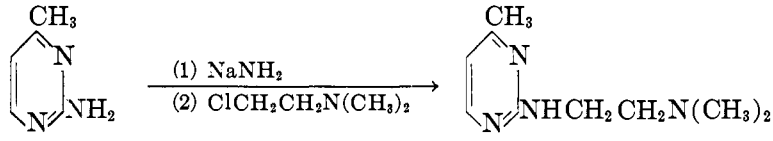
Pyrazine (240, 784) has been aminated by sodium amide. Yields of 33–60 per cent of 2-aminopyrazine were obtained when molten pyrazine was treated at 50–55°C. with sodium amide in a ball-mill reactor in the absence of a solvent (784). Several nuclear-substituted pyrazines have also been aminated by sodium amide (58, 463, 644, 897). Thus, 3-amino-2,5-dimethylpyrazine was obtained in 33 per cent yield by heating 2,5-dimethylpyrazine with sodium amide in dimethylaniline at 165°C. (463).



(33%) (463)

By reaction with sodium amide in liquid ammonia, 2-amino-6-chloro-4-methylpyrimidine is converted to 2-amino-4-methylpyrimidine (529). The reaction mixture obtained from heating 6-methylpyrimidine and sodium amide in decalin was shown to contain 2-amino-6-methylpyrimidine and 2,4-diamino-6-methylpyrimidine (676).

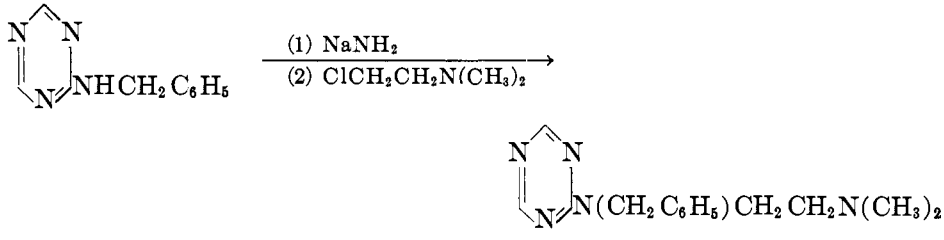
2-Aminopyrimidine (6, 259, 497, 559, 584), a few nuclear-substituted 2-aminopyrimidines (6, 444, 562), and several *N*-substituted 2-aminopyrimidines (298, 483, 486) have been condensed with dialkylaminoalkyl halides (6, 298, 444, 483, 486, 559, 562), benzyl halides (497, 584), thenyl halides (497), and 2-chlorothiazole (259).



(51%) (562)

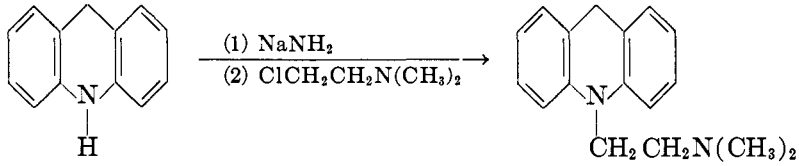
E. TRIAZINES

2-Dimethylaminoethyl chloride has been used to alkylate the sodium derivatives of 2-benzylamino-*s*-triazine, 2-*p*-methoxy(and ethoxy)benzylamino-*s*-triazine, and 2-benzylamino-4-methyl-*s*-triazine (414).



F. OTHER HETEROCYCLIC NITROGEN SYSTEMS

The reaction of acridine with sodium amide in refluxing dimethylaniline gives 9-aminoacridine (72 per cent) (57). 10-Sodioacridan and 9-methyl-10-lithioacridan have been alkylated with 2-diethylaminoethyl chloride (612, 613).



(612)

The sodium derivative of 3-hydroxy-1-phenylpiperidine has been etherified with methyl iodide (686). 1-Ethyl-4-sodioaminopiperidine has been alkylated with 2-diethylaminoethyl chloride (724).

1-(*p*-Chlorobenzhydryl)-4-sodiopiperazine has been alkylated with *p*-methoxybenzyl chloride to give 1-(*p*-chlorobenzhydryl)-4-(*p*-methoxybenzyl)piperazine (617).

1-Methyl- and 5,6,7,8-tetrahydrophenanthridines have been aminated by sodium amide in refluxing diethylaniline to give 9-amino-1-methyl- and 9-amino-5,6,7,8-tetrahydrophenanthridine, respectively (424).

Heating quinoxaline with sodium amide in refluxing dimethylaniline gave a mixture of 2,2′-biquinoxalyl and 2,3-dihydroxyquinoxaline (698). The sodium derivatives of 7-acetamido-5,6-benzoquinoxaline (505) and 2-(*p*-tolylsulfonamido)benzocinnoline (506) have been alkylated with 2-diethylaminoethyl chloride on their amide nitrogen atoms.

XVIII. Sulfones and Related Compounds

By reaction with sodium amide, bromotris(methylsulfonyl)methane is converted to tris(methylsulfonyl)methane (42).

Ethyl benzhydryl sulfone has been alkylated with a number of dialkylaminoalkyl halides (512), several alkyl benzyl sulfones have been condensed with 2-bromopyridine (558), and methyl and benzyl phenyl sulfones have been alkylated with methylbis(2-chloroethyl)amine (278). Two typical examples follow.

$$C_6H_5CH_2SO_2C_2H_5 \xrightarrow[(2)\ 2\text{-bromopyridine}]{(1)\ NaNH_2} C_6H_5CHSO_2C_2H_5(C_5H_4N\text{–}2)$$

(41%) (558)

$$CH_3SO_2C_6H_5 + CH_3N(CH_2CH_2Cl)_2 \xrightarrow{NaNH_2}$$

$$2NaCl + CH_3N\langle\ \rangle SO_2C_6H_5$$

(278)

N,*N*-Diethylmethanesulfonamide has been alkylated with 2-diethylaminoethyl chloride (274) and methylbis(2-chloroethyl)amine (278).

Bradley (125) has found that certain diaryl sulfones and aryl alkyl sulfones are cleaved by sodiopiperidine to give *N*-arylpiperidines and sulfinic acids. Al-

$$(C_6H_5)_2SO_2 + \langle\ \rangle N\text{—}Na \rightarrow C_6H_5SO_2Na + \langle\ \rangle N\text{—}C_6H_5$$

(75%)

though phenyl benzyl sulfone is cleaved by sodiopiperidine to give a mixture of *N*-phenylpiperidine and benzylsulfinic acid, dibenzyl sulfone is recovered unchanged when treated similarly.

Martin (574) treated *o*-bromophenyl methyl sulfone with sodium amide in liquid ammonia and obtained the rearranged product, *m*-aminophenyl methyl sulfone.

XIX. Organosilicon Compounds

A 78 per cent yield of *N*-methylhexamethyldisilazane (II) and some methylamine were obtained by distilling the reaction mixture obtained from heating chloromethyltrimethylsilane, sodium amide, and liquid ammonia in an autoclave at 120°C. for 1.5 hr. (643). It is probable that methyl(trimethylsilyl)amine (I) is formed and decomposes to II on distillation.

$$(CH_3)_3SiCH_2Cl + NaNH_2 \rightarrow \underset{\text{I}}{(CH_3)_3SiNHCH_3} + NaCl$$

$$2\text{I} \xrightarrow{\text{distillation}} \underset{\text{II}}{[(CH_3)_3Si]_2NCH_3} + CH_3NH_2$$

Hauser and Hance (372, 381, 382) have studied the synthesis and the potassium amide-induced cleavage of a number of tetrasubstituted silanes and have proposed a mechanism for these cleavages. Benzyltrimethylsilane was cleaved

$$(C_6H_5)_2CHK + (CH_3)_3SiCl \rightarrow KCl + \underset{\text{III}}{(C_6H_5)_2CHSi(CH_3)_3}$$

(60%) (381)

$$(C_6H_5)_3CK + (CH_3)_3SiCl \rightarrow KCl + \underset{\text{IV}}{(C_6H_5)_3CSi(CH_3)_3}$$

(28%) (381)

by potassium amide in liquid ammonia into toluene (77 per cent), hexamethyldisilazane (14 per cent), and an azeotropic mixture of trimethylsilanol and hexamethyldisiloxane (43 per cent). When III and IV were cleaved, diphenylmethane (90 per cent) and triphenylmethane (91 per cent) were obtained.

XX. Miscellaneous Reactions

A patent has been issued for the preparation of free guanylurea by treating its sulfate with sodium amide in liquid ammonia and then evaporating the solvent (413).

When spruce wood meal is treated with sodium amide in liquid ammonia (297), about half of it becomes soluble in aqueous alkali. The soluble portion contains about two-thirds of the lignin present in the wood.

A patent has been issued (611) for the treatment of carbohydrate material with potassium amide in liquid ammonia to produce an intermediate for esterification. Bley (108) has found that partially alkylated cellulose derivatives may be further alkylated when treated with sodium amide in liquid ammonia, followed by the addition of alkyl halides.

Gardner (303) has reported that attempts to prepare 6-aminocellulose by the reaction of sodium amide in liquid ammonia on 6-iodotosylcellulose acetate have given only traces of nitrogen-containing material.

A cellulose monoamine containing 8.1 per cent of amino nitrogen has been prepared by the reaction of cellulose nitrate with sodium amide or potassium amide in liquid ammonia (753).

Corn starch, amylose, and amylopectin may be converted to their trimethyl and triethyl ethers by reaction with sodium amide and methyl or ethyl iodide in liquid ammonia (416).

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