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THE CHEMISTRY OF THE ALKALI AMIDES. II

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CONTENTS[1]

Part I. Preparation, Storage, and Inorganic Reactions

Part II. Organic Reactions

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[1] The heading numbers are essentially those of the previous review of this subject (Chem. Rev. **12**, 43–179 (1933)).

PART I. PREPARATION, STORAGE, AND INORGANIC REACTIONS

I. INTRODUCTION

The rapid rise in the use of the alkali amides in industry and in the synthetic organic laboratory, as well as the scientific interest attendant upon these compounds, prompted a few years ago the preparation of a complete review of the literature bearing on this topic (14). Since that time (1932) activity in this field has continued, and several important papers have appeared. Also it is now evident that some omissions of past work were made in the original review. Hence it seems desirable to supplement the former by making the necessary additions and by bringing it up to date. The same organization of data will be followed in the supplement so that cross reference may be readily accomplished.

II. HISTORICAL

Wöhler (90) states that both Berzelius (16) and Gmelin (37), on the basis of the results of Gay-Lussac and Thénard (35), showed that the alkali amides had the formula MNH_2. One gathers the impression from Wöhler's paper that these demonstrations were made before Gay-Lussac and Thénard were certain in their own minds of the true formula of these compounds. The question was important to Wöhler because he had just prepared certain amide compounds of tungsten.

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

Action on indicators; neutralization reactions

Fredenhagen (34) has discussed the behavior of indicators toward liquid ammonia solutions of potassium amide and has found the potential of the following cell,

$$H_2 \mid 0.1\ N\ NH_4NO_3 \mid 0.1\ N\ KNH_2 \mid H_2$$

to be 0.746 volt.

By means of a liquid ammonia calorimeter, Kraus and Ridderhof (59) have determined the energies at −33.4°C. of the reactions represented by the following equations:

$$NH_4Br + NaNH_2 = NaBr\cdot am + 2NH_3\ (liq.) - 33{,}000\ cal.$$

$$NH_4Br + KNH_2\cdot am. = KBr\cdot am + 2NH_3\ (liq.) - 27{,}500\ cal.$$

Introducing the energy change accompanying the solution of sodium bromide in liquid ammonia (−9500 cal.) into the first equation, one obtains the energy equation,

$$NH_4Br + NaNH_2 = NaBr + 2NH_3\ (liq.) - 23{,}500\ cal.$$

from which one computes the heat of formation of liquid ammonia at −33.4°C. to be 17,000 cal. Similarly one obtains the equation,

$$NH_4Br\cdot am + KNH_2\ \cdot am = KBr\cdot am + 2NH_3 - 19{,}400\ cal.$$

which shows that the heat of neutralization of an ammono acid by an ammono base in liquid ammonia is much larger than the heat of neutralization of strong acids and bases in water.

Precipitation of insoluble bases

The interaction of potassium amide and barium bromide produces barium amide (47). Liquid ammonia solutions of zirconium bromide and potassium amide (not in excess) produce an equimolecular mixture of $Zr(NH)_2$ and $Zr(NH)NK$ (96).

Amphoteric amides

In addition to the salts of amphoteric amides listed previously (14, p. 51), the following have been prepared: a stannate, $Sn(NK)_2 \cdot 4NH_3$ (11, 31); a stannite, $SnNK \cdot 2NH_3$ (9); a titanate, $NTiNHK$ (77); two zirconates, $Zr(NK)_2NH_3$ and $Zr(NH)NK$; and two thorates, $Th(NK)_2 \cdot KNH_2$ and $Th(NH)NK \cdot NH_3$ (96).

IV. PREPARATION OF THE ALKALI AMIDES

In preparing sodium amide by the interaction of molten sodium and gaseous ammonia, it is essential that the containing vessel be constructed of a material which is not attacked by the molten amide (14, pp. 54–5). Copper vessels have been found to be satisfactory for the preparation of sodium amide (78). The preparation, manipulation, and storage of sodium amide recently has been described in some detail (36). Certain substances, notably sodium hydroxide (78), sodium oxide, and the metals, alloys, oxides, and oxygen salts of the chromium and adjacent groups of metals, exert a catalytic effect upon the reaction between molten sodium and gaseous ammonia (103, 107). Such catalysts are used to facilitate the manufacture of sodium amide in large quantities.

The reaction between liquid ammonia and dissolved alkali metals is very susceptible to catalytic effects (14, pp. 58–9). For the rapid preparation of sodium amide, Vaughn, Vogt, and Nieuwland (82) recommend the use of ammonia-soluble iron (cf. 105), nickel, or cobalt salts (usually the nitrates, which are reduced to the free metals by the sodium) in the presence of sodium oxides. Iron is approximately 40 per cent more efficient than nickel and 20 per cent more than cobalt, while sodium hydroxide is a pronounced, though weak, negative catalyst. Calcium amide could not be prepared by the above procedure, although finely divided silver is an effective catalyst (19). Burgess and Smoker (18; cf. 7) have pointed out the catalytic effect of metallic manganese on the reaction between liquid ammonia and dissolved sodium. Magnesium (6, 10), aluminum (6, 8), beryllium (12), and silver (19) act as catalysts for the interaction of liquid ammonia and dissolved sodium and potassium metals, although the catalytic activity of some metals in the compact form appears to be very low (99, 106). Ferric oxide has been much used as a catalyst for the preparation of potassium amide. Bergstrom (13) has shown that this oxide is a more effective catalyst for the above reaction than either metallic iron or platinum. Ignited cobalt oxide (Co_3O_4) is also an excellent catalyst for the potassium–ammonia reaction. The use of these oxides as catalysts is not to be recommended for producing an amide of highest purity, because of interaction between the oxides and potassium amide.

During the last few years the possibility of preparing sodium amide by the electrolysis of a liquid ammonia solution of sodium chloride has been investigated in some detail (1, 3, 83, 98). Sodium amide is obtained similarly in the electrolysis of sodium nitrate (2) and sodium nitrite (4).

The alkali amides are frequently formed as products of the reducing action of the alkali metals on organic compounds in liquid ammonia (56). The following examples illustrate this type of reaction (cf. 24, 30, 92):

Hydrocarbons

$$\underset{\text{Isoprene}}{C_5H_8} + 2Na + 2NH_3 \rightarrow C_5H_{10} + 2NaNH_2 \quad (68)$$

$$\underset{\text{Styrene}}{C_6H_5CH{=}CH_2} + 2Na + 2NH_3 \rightarrow C_6H_5CH_2CH_3 + 2NaNH_2 \quad (61, 64, 95)$$

$$(C_6H_5)_2C{=}CH_2 + 2Na + NH_3 \rightarrow (C_6H_5)_2CNaCH_3 + NaNH_2 \quad (95)$$

$$C_6H_5CH{=}CHC_6H_5 + 2Na(K) + 2NH_3 \rightarrow C_6H_5CH_2CH_2C_6H_5 + 2Na(K)NH_2 \quad (95)$$

$$(C_6H_5)_2C{=}CHC_6H_5 + 2Na(K) + NH_3 \rightarrow (C_6H_5)_2CNa(K)CH_2C_6H_5 + Na(K)NH_2 \quad (94, 95)$$

$$(C_6H_5)_2C{=}CHCH_3 + 2Na(K) + NH_3 \rightarrow (C_6H_5)_2CNa(K)CH_2CH_3 + Na(K)NH_2 \quad (94, 95)$$

$$(C_6H_5)_2C{=}CHCH(C_6H_5)_2 + 2Na + NH_3 \rightarrow (C_6H_5)_2CNaCH_2CH(C_6H_5)_2 + NaNH_2 \quad (95)$$

$$(C_6H_5)_2C{=}C{=}C(C_6H_5)_2 + 4Na(K) + 2NH_3 \rightarrow (C_6H_5)_2CNa(K)CH_2CNa(K)(C_6H_5)_2 + 2Na(K)NH_2 \quad (95)$$

$$3C_6H_5C{\equiv}CH + 4Na + 2NH_3 \rightarrow 2C_6H_5C{\equiv}CNa + C_6H_5C_2H_5 + 2NaNH_2 \quad (61, 64)$$

$$C_{10}H_8(\text{naphthalene}) + 4Na \rightarrow C_{10}H_8Na_4$$
$$C_{10}H_8Na_4 + 4NH_3 \rightarrow C_{10}H_{12} + 4NaNH_2 \quad (62, 93)$$

$$\underset{\text{Anthracene}}{C_{14}H_{10}} + 2Na + 2NH_3 \rightarrow C_{14}H_{12} + 2NaNH_2 \quad (63)$$

Halides

$$RX(R = \text{alkyl}) + 2Na + NH_3 \rightarrow RH + NaX + NaNH_2 \quad (20, 23, 27, 91)$$

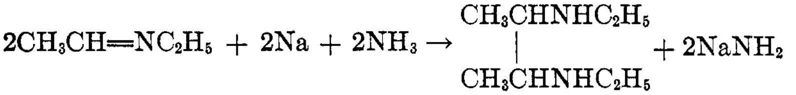
$NaNH_2$ is formed during the similar reduction of certain paraffin polyhalides (21, 22, 23).

Naphthols

$$C_{10}H_7OH + 4Na + 3NH_3 \rightarrow C_{10}H_{11}ONa + 3NaNH_2 \quad (87)$$

Nitrogen compounds

$$(C_6H_5)_3CNH_2 + 2Na(K) \rightarrow (C_6H_5)_3CNa(K) + Na(K)NH_2 \quad (51)$$



$$2CH_3CH{=}NC_2H_5 + 2Na + 2NH_3 \rightarrow \begin{array}{c} CH_3CHNHC_2H_5 \\ | \\ CH_3CHNHC_2H_5 \end{array} + 2NaNH_2 \quad (72)$$

$$C_6H_5NO_2 + 4Na + NH_3 \rightarrow C_6H_5Na(ONa) + NaNH_2 \quad (86)$$

$$C_6H_5NH(OH) + 2Na + NH_3 \rightarrow C_6H_5NH_2 + NaOH + NaNH_2 \quad (86)$$

$$C_6H_5NO{:}NC_6H_5 + 2Na + NH_3 \rightarrow C_6H_5N{=}NC_6H_5 + NaOH + NaNH_2 \quad (86)$$

Sulfides

$$R_2S + 2Na + NH_3 \rightarrow NaSR + RH + NaNH_2 \quad (89)$$

Metallo-organic compounds

$$C_2H_5HgCl + 3Na + NH_3 \rightarrow C_2H_6 + NaCl + NaHg + NaNH_2 \quad (49)$$

$$(C_6H_5)_4Ge + 2Na + NH_3 \rightarrow NaGe(C_6H_5)_3 + C_6H_6 + NaNH_2 \quad (53)$$

$$\begin{array}{l} [(C_2H_5)_3Ge]_2 + 2Li \rightarrow 2LiGe(C_2H_5)_3 \\ LiGe(C_2H_5)_3 + NH_3 \rightarrow HGe(C_2H_5)_3 + LiNH_2 \quad (58) \end{array}$$

$$(CH_3)_4Sn + 2Na + NH_3 \rightarrow (CH_3)_3SnNa + CH_4 + NaNH_2 \quad (50, 54)$$

$$(CH_3)_3SnNH_2 + 2Na \rightarrow (CH_3)_3SnNa + NaNH_2 \quad (54)$$

$$[(CH_3)_3Sn]_2CH_2 + 4Na + 2NH_3 \rightarrow 2NaSn(CH_3)_3 + CH_4 + 2NaNH_2 \quad (54)$$

$$\begin{array}{l} (CH_3)_3SnCH{=}CHSn(CH_3)_3 + 4Na + 2NH_3 \rightarrow NaSn(CH_3)_3 + \\ \qquad NaSn(CH_3)_2CH{=}CH_2 + CH_4 + 2NaNH_2 \quad (55) \end{array}$$

$$\begin{array}{l} (C_6H_5)_4Sn + 2Na + NH_3 \rightarrow (C_6H_5)_3SnNa + C_6H_6 + NaNH_2 \\ (C_6H_5)_3SnNa + 2Na + NH_3 \rightarrow (C_6H_5)_2SnNa_2 + C_6H_6 + NaNH_2 \quad (25) \end{array}$$

A similar reaction in the inorganic field has also been reported (41):

$$6Na + 3NH_3 + 2P \rightarrow Na_3P \cdot PH_3 + 3NaNH_2$$

The alkali amides are also products of the ammonolysis of the monoxides, $M_2O + NH_3 \rightarrow MNH_2 + MOH$ (75): $NaNH_2$ (45, 52), KNH_2 (52, cf. 60), $CsNH_2$ (73, 74). This reaction is the initial one in the slow oxidation of the alkali metals in liquid ammonia. A closely related reaction is that of nitrous oxide upon solutions of sodium and potassium:

$$N_2O + 2M + NH_3 \rightarrow MNH_2 + MOH + N_2 \quad (46, 48)$$

Finally, sodium nitride is ammonolyzed to the amide by gaseous or liquid ammonia (84):

$$Na_3N + 2NH_3 \rightarrow 3NaNH_2$$

Sodium amide has been reported as a reduction product of sodium azide (39, 88):

$$NaN_3 + 4H_2 \rightarrow NaNH_2 + 2NH_3$$

Patents dealing with the manufacture of the alkali amides include those covering the use of the catalysts previously mentioned, the preparation of a solution of sodium amide in sodium hydroxide (102), and the preparation of finely divided, reactive sodium amide (110) by stirring the amide in the presence of a diluent before it congeals.

V. PROPERTIES OF THE ALKALI AMIDES

Mentrel (66) has given the following observations on the behavior of the alkali amides: Molten sodium amide in contact with gaseous ammonia is a bright green liquid. At 500°C. it darkens and vigorously evolves nitrogen and hydrogen; the amide is regenerated upon cooling in an ammonia atmosphere. In a vacuum decomposition begins at 330°C. and is complete at 440°C., sodium metal remaining. At 390°C. gas evolution is slow and a mixture of sodium nitride (?), sodium, and sodium amide is left. Below 400°C. lithium amide is a bright green liquid, becoming reddish at 430°C. and evolving nitrogen and hydrogen. In a vacuum gassing begins at 370°C.; at 450°C. lithium imide, or a mixture of the nitride and amide, is left. Between 750° and 800°C. decomposition into lithium and ammonia is complete. Lithium and lithium amide in a vacuum at 460°C. do not give the imide.

Patents have been issued for the preparation of water-free caustic alkalis by the action of water on the alkali metal amides (100). In the preparation of metallic sodium by the electrolysis of fused sodium hydroxide, Moltkehansen (109) claims that the addition of sodium amide has a desirable effect. The presence of sodium amide not only lowers the melting point of the electrolyte bath very much, but also suppresses the secondary reaction between sodium and water at the cathode with formation of hydrogen. Instead of diffusing through the electrolyte, the water arising from the discharge of the hydroxyl ion,

$$2HO^- \rightarrow H_2O + 1/2\ O_2$$

is fixed with the liberation of ammonia,

$$NaNH_2 + H_2O \rightarrow NaOH + NH_3$$

As a result of greatly improved methods, older values for the conductances of the amides of sodium and potassium in liquid ammonia have been corrected by the work of Hawes (38; cf. 57) and the concentration range has been extended. The data obtained for sodium amide do not agree with the simple mass action or more refined theories, possibly because of the small size of the amide ion. Somewhat better agreement was found in the case of potassium amide.

Whereas Franklin (33) has given the solubility of sodium amide as 1 g. per liter (14, p. 60), Hunt and Boncyk (42) report the value of 0.004 g. per 100 g. of ammonia. Since the latter determination was made on a commercial sample (usually very impure) of the amide (43), the result may well be questioned. The validity of Franklin's value is substantiated by the conductance work of Hawes (38), who found that at −33°C. saturation is attained at approximately 50 liters (0.8 g. of sodium amide per 1000 cc. of ammonia). A variety of sodium amide has been reported which is soluble to the extent of approximately 1 mole per liter at −33°C. (82). The solubility of potassium amide at 25°C. is given as 3.6 g. per 100 g. of ammonia (42).

VI. DETERIORATION OF THE AMIDES DURING STORAGE

Bouveault and Levallois (17) state: "It is highly desirable to powder sodium amide under dry ether or benzene. For lack of this precaution we had a rather curious accident. When the amide contains some sodium nitrite (which is not rare) and accidentally a bit of sodium, the rise in temperature produced by grinding in the presence of air produces a violent combustion." Other investigators (40) report that sodium amide kept poorly sealed explodes when fused with organic substances. These observations support the recommendations previously made (14, pp. 64–5) for storing the amides. A patent (112) has been granted for the preparation of mixtures which can be safely handled and transported by grinding an alkali amide with two to six times its weight of an inert organic liquid, e.g., benzene, until a homogeneous paste is obtained.

VIII. THE NATURE OF THE FUSED AMIDES

A patent has been granted for the preparation of the alkali metals by the electrolysis of their molten amides (101).

IX. REACTIONS OF THE ELEMENTS WITH THE ALKALI AMIDES

Group I, Subgroup B

Copper. Vessels of copper are not attacked by fused sodium amide (78).

Group II, Subgroup B

Indium. Indium is not attacked by a solution of potassium amide in liquid ammonia (29).

Group IV, Subgroup B

Carbon. Perhaps the earliest reference to the formation of cyanides by the action of carbon upon sodium amide is that of Drechsel (28), who gives the equation

$$NaNH_2 + C \rightarrow NaCN + H_2$$

He also states that potassium cyanamide is reduced to the cyanide by carbon.

Germanium. Germanium is not attacked by a liquid ammonia solution of potassium amide (97).

Tin; lead. Bergstrom's work on the action of liquid ammonia solutions of potassium amide upon tin and lead has recently been confirmed (97).

Group VI, Subgroup B

Sulfur. The following reactions have been found to occur at −33°C. between potassium amide and sulfur in liquid ammonia solution (15):

Potassium amide in excess:

$$6KNH_2 + 3S \rightarrow 2K_2S + S(NK)_2 \cdot NH_3 + 3NH_3$$

$$S(NK)_2 \cdot NH_3 + \text{heat} \rightarrow S(NK)_2 + NH_3$$

Sulfur in excess:

$$6KNH_2 + 12S \rightarrow 2K_2S_4 + S_4(NK)_2 + 4NH_3 \text{ (rapid operations)}$$

$$6KNH_2 + 10S \rightarrow 2K_2S_3 + S_4(NK)_2 + 4NH_3 \text{ (slow operations)}$$

Group VII, Subgroup B

Iodine. Ruff (76) reports the formation of a salt, Na_2NI_3, when sodium amide and iodine react in liquid ammonia.

The reaction,

$$N_2O + 2MNH_2 \rightarrow MN_3 + NH_3$$

takes place in liquid ammonia with both sodium and potassium amides (46, 48; cf. 5). The reaction between finely divided sodium amide and nitrous oxide is used for the commercial preparation of azides (104, 108, 111).

Nitric oxide, under pressure, reacts with potassium amide in solid ammonia to give a series of products which may be regarded as arising through the following reactions (79):

$$\begin{aligned} KNH_2 + NO &\rightarrow KNO + NH_2 \\ 2NH_2 &\rightarrow H_4N_2 \text{ (larger part)} \\ NH_2 + NO &\rightarrow H_2NNO \text{ (smaller part)} \\ 2H_2NNO &\rightarrow NH_4NO_2 + N_2 \text{ (decomposition by } KNH_2\text{)} \end{aligned}$$

Sodium amide has been used to free a mixture of gaseous hydrogen and nitrogen from traces of moisture, carbon monoxide, and hydrogen sulfide (26). The following reactions are said to take place at 100°C.:

$$CO + 2NaNH_2 \rightarrow CH_4 + Na_2O + N_2$$

$$H_2S + 2NaNH_2 \rightarrow Na_2S + 2NH_3$$

Liquid ammonia, sodium amide, and compressed carbon monoxide are reported to give the sodium salts of hydrocyanic, carbonic, and formic acids (80). On mild heating sodium amide converts potassium cyanate into a salt of cyanamide (28),

$$2NaNH_2 + KNCO \rightarrow KNaCN_2 + NaOH + NH_3$$

At ordinary temperature, sodium amide reacts slowly with carbonyl chloride (in toluene solution) according to the equation,

$$3NaNH_2 + COCl_2 \rightarrow NaNCO + 2NaCl + 2NH_3$$

(see p. 431). At 250°C. the reaction is the following,

$$5NaNH_2 + COCl_2 \rightarrow Na_2CN_2 + 2NaCl + NaOH + 3NH_3$$

although the product contains 13 to 14 per cent of NH_4CN. At 500°C. inflammation occurs with formation of melanurates and their chloro derivatives (69, 70). With sulfuryl chloride, SO_2Cl_2, in toluene solution a 20 per cent yield of trisulfimide results, but no sulfamide. Similarly, with sulfur monochloride in xylene at ordinary temperature, sulfur and sulfur nitride are formed, but at 120°C., in the absence of air, the reaction is represented by

$$12NaNH_2 + 3S_2Cl_2 \rightarrow 2Na_2S_2 + 8NH_3 + 6NaCl + 2N_2 \qquad (69)$$

The compound $\overline{N{:}SH \cdot N{:}SH \cdot N{:}SH \cdot N{:}S}H$ (tetrathioltetrazole) forms with potassium amide in liquid ammonia a compound, $KSN \cdot KNH_2$, which is freely soluble in the ammonia if an excess of $(HSN)_4$ is present. So much potassium amide is invariably present in equilibrium that addition of lead iodide precipitates a mixture of $Pb(SN)_2 \cdot NH_3$ with PbNH and $PbN \cdot PbI \cdot NH_3$ (67). The following reactions also have been shown to occur:

$$3NaNH_2 \text{ (solid)} + 2NOCl \rightarrow 2NaCl + NaNO_2 + 2NH_3 + N_2 \qquad (79)$$

$$KNH_2 + ONOSO_3H + NH_3 \rightarrow KNO_2 + H_2NSO_3(NH_4) \qquad (79)$$

$$3NaNH_2 + 2BrCN \rightarrow NaN(CN)_2 + 2NH_3 + 2NaBr \qquad (16a)$$

Franklin (32; cf. 5) has demonstrated that azides may be obtained by heating liquid ammonia solutions of nitrates with the alkali amides. At 80–90°C. potassium nitrate and potassium amide react thus:

$$KNO_3 + 2KNH_2 \rightarrow KN_3 + 3KOH + NH_3$$

Better yields (up to 75 per cent), in a shorter time, result from operating at a higher temperature (130–140°C). At 200°C. or higher, liberal quantities of nitrogen are set free and the yield of potassium azide is lower. By using sodium nitrate and sodium amide, yields of sodium azide up to 16 per cent may be obtained. An 80 per cent yield of lead azide is achieved by heating lead nitrate with an excess of potassium amide in liquid ammonia solution. Stannous chloride forms sodium stannite in molten sodium amide,

$$SnCl_2 + 3NaNH_2 \rightarrow NaNSn + 2NaCl + 2NH_3$$

Sodium amide reacts with anhydrous hydrazine to give a very unstable salt, $NaNH \cdot NH_2$ (81, 85). Sodium amide (not in excess) liberates only trivial amounts of hydrazine from hydrazinium salts (44) in hydrocarbon media.

If silicates, glasses, and certain refractories are ground to pass through a 200-mesh sieve, they can be decomposed by fusion with sodium amide at

300–337°C. A 100-cc. nickel crucible is recommended and an electric muffle through which ammonia gas is passed. After fusing, a complete analysis may be made in the usual way (71).

Lock (65) found that a considerable quantity of gas was evolved when sodium amide was heated to 150°C. in glass vessels.

The reaction of sodium amide with cyanogen is discussed in part II, section XII F (see p. 458).

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Certain additions and corrections should be made in connection with the references given in the earlier paper (14, pp. 80–2):

Ref. 2. *Add:* Beilstein, F., and Geuther, A.: Jahresber. **1858,** 118–21.

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Ref. 26. *Add:* Dennis, L. M., and Browne, A. W.: Z. anorg. Chem. **40**, 82–94 (1904).

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Part II. Organic Reactions

I. INTRODUCTION. PREPARATION

In bringing the review of the chemistry of the alkali amides (6) up to date, it has become apparent that it will be impossible to include all significant references to the literature, because of the difficulty of finding many of the articles which deal only incidentally with this subject. This is particularly true of the organic section. The authors sincerely hope that omissions will be brought to their attention.

Methods of preparing sodium amide have been discussed in the inorganic section of this review (part I), but the following appear to be of interest particularly to organic chemists. Ziegler (165) ground sodium amide with benzene or a similar inert hydrocarbon in a ball mill, obtaining a pasty mass which was very reactive and could be safely transported (cf. 6, p. 137). Shreve (136) has used a steel ball mill for making sodium amide and for the preparation from it of mono- and di-aminopyridines.

Vaughn, Vogt, and Nieuwland (149) have prepared a very reactive sodium amide by adding sodium to a solution of a small quantity of hydrated ferric nitrate in liquid ammonia (see also 126).

Organic substitution products of the alkali metal amides, of the type of lithium diethylamide $(C_2H_5)_2NLi$, have proven to be of considerable value in the preparation of branched-chain aliphatic nitriles, and in the synthesis of large ring systems, such as cyclopentadecanone (see section XII F).

Lithium salts of the primary and secondary aliphatic and secondary aliphatic-aromatic amines are most easily prepared on a laboratory scale by treating the amine with a solution of lithium phenyl or lithium *n*-butyl in absolute ether (166; cf. 6, p. 137). Thus,

$$(C_2H_5)_2NH + LiC_6H_5 \rightarrow C_6H_6 + (C_2H_5)_2NLi$$

$$C_6H_5NHC_2H_5 + LiC_4H_9 \rightarrow C_4H_{10} + C_6H_5NLiC_2H_5$$

Large scale manufacture, however, demands a cheaper method of preparation, and consequently we find several patents in this field during the past few years.

According to Ziegler (161), compounds of the formula MNRR′ (M is an alkali metal, R is an aliphatic or aromatic radical, and R′ is hydrogen or an aliphatic or aromatic radical) are prepared by treating an alkali metal with a primary or secondary aliphatic or secondary aliphatic-aromatic amine in the presence of (a) an alkyl or aryl halide, (b) an unsaturated hydrocarbon having at least two conjugated double bonds, (c) an unsaturated hydrocarbon having an aryl residue linked to an unsaturated carbon atom, or (d) an aromatic hydrocarbon capable of forming addition products with the alkali metals.

Thus lithium, diethylamine, and naphthalene react in ether (atmosphere of nitrogen) to give lithium diethylamide, $(C_2H_5)_2NLi$. Lithium, monoethylaniline, and styrene or butadiene give lithium ethylphenylamide, $C_6H_5N(Li)C_2H_5$. Sodium cyclohexylamide, $C_6H_{11}NHNa$, may be made from sodium, cyclohexylamine, and phenyl chloride.

Lithium and naphthalene react to form an addition compound, which is "aminolyzed" by diethylamine to lithium diethylamide, in the same way that the substance formed by treating naphthalene with sodium in liquid ammonia is ammonolyzed to tetrahydronaphthalene and sodium amide (159, 97a).

The alkali metals add to many double bonds, and particularly to those activated by aryl groups. These addition compounds are "aminolyzed" to metallic derivatives of the amine and the reduced hydrocarbon. Phenyl chloride and sodium in ether are known to give the highly reactive sodium phenyl (110a), and this is doubtless the immediate precursor of sodium cyclohexylamide.

$$C_6H_5Na + C_6H_{11}NH_2 \rightarrow C_6H_6 + C_6H_{11}NHNa$$

II. THE OXIDES OF CARBON AND CARBON DISULFIDE

Carbon monoxide is treated in part I, section X. Carbon disulfide is mentioned in part II, section VIII B.

III. AMMONOCARBONIC ACIDS

The dialkyl cyanamides, R_2NCN, are esters of cyanamide, NH_2CN, an ammonocarbonic acid, and will be considered under section XIII A.

Niemann (as reported by Franklin (47)) found that *N*, *N'*, *N''*-triphenylguanidine (a triphenyl ester of an ammonocarbonic acid, guanidine) forms a dipotassium salt with potassium amide in liquid ammonia at room temperatures, but no further reaction occurs on heating, although one should anticipate ammonolysis to guanidine and aniline. This may, however, be brought about by ammonium chloride in liquid ammonia at 200°C.

Biechler (9) has studied the reactions,

$$3NaNH_2 + 2BrCN \rightarrow NaN(CN)_2 + 2NH_3 + 2NaBr$$

and

$$RN(CN)K + BrCN \rightarrow RN(CN)_2 + 2KBr$$

The first reaction is to be interpreted as the action of a base, sodium amide, on an acid bromide of an ammonocarbonic acid, cyanogen bromide, to give the salt of an ammonocarbonic acid, sodium dicyanimide. Apparently, under the conditions of Biechler's work, the latter is not changed to disodium cyanamide, Na_2CN_2, as in the work of Perret and Perrot (118). Phenyldicyanoimide, *o*-methoxyphenyldicyanoimide, and *p*-tolyldicyanoimide were prepared in accordance with the second equation, but attempts to make the corresponding *o*-tolyl, chlorophenyl, and α-naphthyl derivatives failed. (A mixture of polymers was obtained.)

IV. MIXED AQUOAMMONOCARBONIC ACIDS

Potassium cyanate is treated in part I, section X. Blair and Smith (105), in accumulating evidence for the tautomerism of cyanourea, $NH_2CONHCN$, have prepared an ammonia-soluble monopotassium salt and ammonia-insoluble di- and tri-potassium salts by the action of potassium amide in proper proportion on this aquoammonocarbonic acid in liquid ammonia. The work of Miss Fulton, concerning the formation of monopotassium and monosodium salts of the acid amides in liquid ammonia, and their decomposition into hydrocarbons at elevated temperatures when heated with an excess of alkali amide, has now been published (47a).

Perret and Perrot (118, 119) give the following equations for the reaction between phosgene and sodium amide (see p. 422). In toluene, at ordinary temperatures,

$$3NaNH_2 + COCl_2 \rightarrow NaNCO + 2NaCl + 2NH_3$$

At 250°C., the chief reaction is

$$5NaNH_2 + COCl_2 \rightarrow Na_2CN_2 + 2NaCl + NaOH + 3NH_3$$

but the product contains 13 to 14 per cent of NH_4CN.

V. HYDROCARBONS (ALL CLASSES)

Cook and Hewett (28a) find that 2,3-benzo-1,3,3-bicyclo-Δ^2-nonene does not react with methyl iodide and sodium amide.

Carothers and Jacobson (15, 80) have prepared the sodium salt of vinylacetylene, $CH_2{=}CHC{\equiv}CNa$, with the use of sodium amide, and from it have made 1-(methyl, ethyl, butyl, or heptyl)-2-vinylacetylene.

Lai (96) prepared the sodium salt of *n*-heptyne, $CH_3(CH_2)_4C{\equiv}CNa$, by the action of sodium amide on *n*-heptyne in xylene at 60°C. From this, and from the sodium salts of *n*-octyne and *n*-undecyne, a number of diacetylenes were made by the reaction represented below.

$$RC{\equiv}CNa + R'C{\equiv}CCH_2Br = RC{\equiv}CCH_2C{\equiv}CR' + NaBr$$

Among other compounds, the following were made: heptadecadiyne-7,10; hexadecadiyne-6,9; pentadecadiyne-6,9; and tricosadiyne-6,9. The poor yields (about 20 per cent) were due not only to resinification, but also to the formation of tri- or tetra-acetylenic hydrocarbons.

Mlle. Grédy (56), in connection with her work on Raman spectra, has alkylated the sodium salts of a number of acetylenic hydrocarbons with dimethyl sulfate. A few of the compounds prepared in this manner are 1-cyclopentyl-1-propyne, 1-cyclohexyl-1-propyne, pentyne-2, hexyne-2, heptyne-2, octyne-2, nonyne-2, and 3-phenylpropyne-2.

Bried and Hennion (12b) have prepared diethyl-, dipropyl-, dibutyl-, and diamyl-acetylenes by the action of the corresponding alkyl halide on sodium acetylide and sodium amide in liquid ammonia, without the isolation of the intermediate monoalkylacetylenes.

Vaughn (148a) has prepared propyl-, butyl-, heptyl-, and nonyl-acetylenes from the corresponding alkyl halide and the sodium salt of acetylene in liquid ammonia.

There are recorded a few new illustrations of the Favorsky rearrangement,

$$RC{\equiv}C(CH_2)_nCH_3 \xrightarrow[\text{heat}]{NaNH_2} R(CH_2)_{n+1}C{\equiv}CNa + NH_3$$

in which a disubstituted acetylene is converted by the action of sodium amide at elevated temperatures in an inert medium (mineral oil, etc.) into the sodium salt of a "true" acetylene.

According to Lai (97), the action of sodium amide on tetracosa-10,14-diyne at 160–170°C. liberated ammonia corresponding to a 60 per cent transformation of the diacetylene into an isomeric "true" acetylene. The extreme instability of the latter and consequent resinification prevented its isolation. The isomerization by sodium amide is due to its tendency to form an insoluble salt with the "true" acetylene, and thus the equilibrium mixture of $RC{\equiv}CCH_3$ and $RCH_2C{\equiv}CH$, for example, passes into an irreversible system,

$$RCH_2C{\equiv}CH + NaNH_2 \rightarrow NH_3 + RCH_2C{\equiv}CNa$$

Since Vaughn, Vogt, and Nieuwland (149) were unable to rearrange ethylamylacetylene with sodium amide in liquid ammonia at −33°C. in sixteen hours, a high temperature is apparently necessary. Decylacetylene was prepared in 34 per cent yield by heating diamylacetylene with sodium amide in mineral oil at 210°C., while octylacetylene was similarly prepared from dibutylacetylene (148a).

Guest (58, 59) states that both true acetylenes (i.e., those which contain a $\equiv CH$ group) and isoacetylenes (of the type $RC{\equiv}CR'$) are formed by heating paraffin dihalides with sodium amide; this statement is in disagreement with the views of Bourguel (11), who claims that only true acetylenes are formed. *n*-Heptyne, $CH_3(CH_2)_4C{\equiv}CH$, was rearranged by passing over heated soda lime to a mixture containing a large proportion of isoheptynes. Heated sodium amide, under mineral oil, altered the composition of this mixture to about 65 per cent of the true heptyne.

Kraus and Kahler (93) have made sodium triphenylmethyl, $(C_6H_5)_3CNa$, for conductivity work by the action of sodium amide on triphenylmethane in liquid ammonia.

The action of sodium amide on fluorene (at 150°C.) and indene (at 110–115°C.) gives the corresponding sodium salts (151, 152). Advantage has been taken of this in the separation of fluorene from the coal tar fraction in which it is contained, and in its purification (51). A process has been patented for the preparation of sodium indene with the use of sodium amide or sodium metal and dry ammonia (52).

VI. HALOGEN COMPOUNDS

A. Paraffin monohalides

Horning (74) obtained cyclohexene in 65 per cent yield by treating cyclohexyl chloride with potassium amide in liquid ammonia. He also prepared diethyl-*n*-butylamine in absolute ether in accordance with the equation,

$$\mathrm{LiN(C_2H_5)_2} + n\text{-}\mathrm{C_4H_9Br} \rightarrow \mathrm{LiBr} + n\text{-}\mathrm{C_4H_9N(C_2H_5)_2}$$

B. Unsaturated monohalides

A very convenient method for preparing acetylenic hydrocarbons has been discussed in the previous review (6, pp. 92–8), and is expressed by the equations,

$$\mathrm{RCCl{=}CH_2} + 2\mathrm{NaNH_2} \rightarrow \mathrm{RC{\equiv}CNa} + \mathrm{NaCl} + 2\mathrm{NH_3}$$

$$\mathrm{RCH{=}CHCl} + 2\mathrm{NaNH_2} \rightarrow \mathrm{RC{\equiv}CNa} + \mathrm{NaCl} + 2\mathrm{NH_3}$$

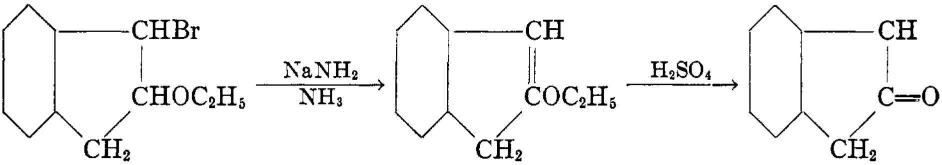
If the reaction yields a disubstituted acetylene, with at least one of the substituents an alkyl group, the Favorsky rearrangement may occur, yielding a true acetylene (see section V).

Thus, Davis and Marvel (34) prepared 3-ethyl-3-methylpentyne-1 in 75 per cent yield by heating sodium amide with 3-ethyl-3-methyl-2-chloropentene-1 in mineral oil at 160–175°C. Ozanne and Marvel (117) have used the method of Lespieau and Bourguel (98) to prepare $\mathrm{(CH_3)_3CCH_2C{\equiv}CH}$ from $\mathrm{(CH_3)_3CCH_2CBr{=}CH_2}$ and sodium amide. Mlle. Grédy (56, 57) treated the mixture of halides resulting from the action of phosphorus pentachloride on methyl isopropyl ketone with sodium amide at 150°C., obtaining isopropylacetylene in poor yield. Guest (58, 59) has made use of this method in the synthesis of some acetylenes, as has previously been described in section V. Lewinsohn (99) similarly prepared *n*-heptyne.

According to Vaughn, Vogt, and Nieuwland (149), sodium amide, prepared in liquid ammonia at −33°C. by the action of ammonia on sodium in the presence of hydrated ferric nitrate as a catalyst, readily removes hydrogen halide from suitably constituted compounds to give acetylenes. Thus, 2-bromoöctene-1 is converted in 73 per cent yield to hexylacetylene, β-bromostyrene in 75 per cent yield to phenylacetylene, and 2-iodohexene-1 in 31 per cent yield to *n*-butylacetylene.

Mlle. Grédy (57) has used the sodium amide method for the preparation of a number of acetylenic hydrocarbons from unsaturated halides, having synthesized, among other compounds, the following: isopropylacetylene from $(CH_3)_2CHCBr{=}CH_2$, 3-cyclopentyl-1-propyne from 3-cyclopentyl-2-bromo-Δ^1-propene (in decalin), and cyclohexylacetylene.

Porter and Suter (122) removed the elements of hydrobromic acid from 1-ethoxy-2-bromoindane with sodium amide in liquid ammonia at −33°C., forming an enol ether, which gave 1-indanone after hydrolysis.



Coleman, with Maxwell and Holst, has examined the reaction of potassium amide, dissolved in liquid ammonia, with a number of chloroethenes and bromoethenes. In all cases hydrogen halide is readily removed, but in so doing there is a rearrangement to give a substituted tolane, or diphenylacetylene. Thus,

$$(C_6H_5)_2C{=}CHCl + KNH_2 \rightarrow KCl + NH_3 + \underset{\text{Tolane}}{C_6H_5C{\equiv}CC_6H_5}$$

An *o*-, *m*-, or *p*-substituted phenyl in the chloro- or bromo-ethene appears in the same configuration in the product. As an illustration, 1,1-di-*o*-tolylbromoethene and potassium amide give di-*o*-tolylacetylene.

These reactions are interpreted as involving, first, the removal of halide ion from the diarylchloro- or bromo-ethene, leaving a carbon atom with a sextet of electrons. A pair of electrons is attracted from the neighboring carbon atom, the aryl group held by the shifting electrons moving with it. An electron pair then shifts to give a triple bond, liberating a proton and forming the tolane. The yields of crude tolanes exceeded 90 per cent of the theoretical, with the exception of those containing *p*-ethylphenyl, *p*-*n*-propylphenyl, and *p*-*n*-butylphenyl groups, where 60 per cent appeared to be the maximum yield (26, 27, 28).

C. Paraffin polyhalides

Dihalides of the type of ethylene dibromide, with halogens on adjacent carbon atoms, in general react with the alkali amides to form acetylenes. Thus, Vaughn, Vogt, and Nieuwland (149) have made stilbene from stilbene dibromide and sodium amide in liquid ammonia in 86 per cent yield. *n*-Amylacetylene and *n*-octylacetylene are similarly formed in approximately 55 per cent yield from 1,2-dibromoheptane and 1,2-dibromodecane, respectively.

Guest (58), in disagreement with Bourguel (11), finds that sodium amide reacts with dihalides to give isoacetylenes as well as "true" acetylenes, as in the reaction,

$$CH_3CH_2CH_2CH_2CH_2CH_2CHCl_2 \xrightarrow[\text{toluene or xylene}]{NaNH_2\text{ in boiling}} \begin{matrix} n\text{-heptyne, 70 per cent} \\ \text{isoheptynes, 30 per cent} \end{matrix}$$

1,2-Dibromobutane reacts with sodium amide in kerosene at 145°C. to give the sodium salt of an acetylene, which, after carbonation, becomes ethylpropiolic acid, $C_2H_5C{\equiv}CCOOH$ (42) (2 to 3 per cent yield).

Titanium trichloride and *tert*-butylethinylcarbinol react to form a dihalide, $C_{38}H_{56}Cl_2$, which, with sodium amide in xylene, gives a hydrocarbon, $C_{38}H_{54}$, of unknown constitution (144).

Propylidene dichloride and sodium amide in paraffin oil give methylacetylene in poor yield (75).

Divinyl ether is formed only to the extent of 3 per cent by the action of sodium amide on β,β'-dichloro(or diiodo)ethyl ether in xylene at its boiling point (125). Hexafluoroethane reacts violently with sodium amide at 250°C., but no products have been isolated (143).

D. Aromatic halides

Phenylacetylene is formed in yields of 75 per cent and 57 per cent, respectively, by treating β-bromostyrene and α-chlorostyrene with sodium amide in liquid ammonia (149).

According to a German patent (105), chlorobenzene reacts with sodium amide at 110–120°C., in the presence of copper gauze or copper powder, to give triphenylamine, while under similar conditions tribenzylamine is obtained from benzyl chloride and triisoamylamine from isoamyl chloride. Mixtures of chlorine compounds and a primary amine may be heated with sodium amide, when, if the amine contains a different radical, a mixed tertiary amine results. Thus, benzyl chloride and *p*-toluidine give dibenzyl-*p*-toluidine, while aniline and benzyl chloride give dibenzylaniline. On the other hand, a solution of potassium amide in liquid ammonia converts benzyl chloride either to stilbene, $C_6H_5CH{=}CHC_6H_5$, or to a compound of the composition $(C_7H_6)_4$ and m.p. 144°C., depending upon the conditions. Other substances are formed in this reaction, whose mechanism is at present imperfectly understood (124, 148).

Chloro-, bromo-, and iodo-benzenes (fluorobenzene is inert) react very rapidly with a liquid ammonia solution of potassium amide at −33°C. to give aniline and diphenylamine, with smaller quantities of triphenylamine and *p*-aminobiphenyl, in proportions which depend upon the experimental conditions (7). In boiling ether or benzene the above reactions either do not occur, or else are very slow.

The formation of potassium anilide, or potassium diphenylamide, in accordance with equations 1 and 5 below is very rapid in comparison with the primary replacement of halogen (equation 1). Consequently, when potassium amide is added to an excess of a phenyl halide, halide ion is formed only to the extent of 50 to 60 per cent of the theoretical, calculated on the basis of the potassium. Competition reactions indicate the following order of ease of replacement of halogen in the unsubstituted phenyl halides: $Br > I > Cl >>> F$. The same order is found for replacements involving the phenyl dihalides of the type $p\text{-}C_6H_4XY$.

The reactions, insofar as is known at the present time, are expressed by the following equations (160),

$$C_6H_5Br + KNH_2 \rightarrow C_6H_5NH_2 + KBr \tag{1}$$

$$C_6H_5NH_2 + KNH_2 \rightarrow C_6H_5NHK + NH_3 \tag{2}$$

$$C_6H_5NHK + C_6H_5Br \xrightarrow{NH_2^-} (C_6H_5)_2NH + KBr \tag{3}$$

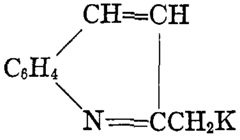
$$C_6H_5NHK + C_6H_5Br \xrightarrow{NH_2^-} p\text{-}C_6H_5C_6H_4NH_2 + KBr \tag{4}$$

$$(C_6H_5)_2NH + KNH_2 \rightarrow (C_6H_5)_2NK + NH_3 \tag{5}$$

$$(C_6H_5)_2NK + C_6H_5Br \xrightarrow{NH_2^-} (C_6H_5)_3N + KBr \tag{6}$$

It is interesting to observe that reactions 3, 4, and 6 are rapid only in the presence of an excess of amide ions, that is to say, of an excess of potassium amide. This peculiar form of catalysis has yet to receive a satisfactory explanation.

Potassium triphenylmethyl, $(C_6H_5)_3CK$, reacts more rapidly with chlorobenzene in the presence of potassium amide than in its absence, tetraphenylmethane, $(C_6H_5)_4C$, being formed. Addition of potassium amide to a solution of chlorobenzene and potassium quinaldyl,



in liquid ammonia gives 2-benzylquinoline, 2-benzohydrylquinoline, and 2-triphenylmethylquinoline, all three hydrogen atoms of the methyl group of quinaldine having been replaced by phenyl. The structure of the last two has not yet been proven by independent synthesis.

Only the strongest bases in the Brønsted sense (i.e., the strongest anions), NH_2^-, $(C_6H_5)_2CH^-$, and $(C_6H_5)_3C^-$, react with the phenyl halides in liquid ammonia at −33°C., and the last two only react slowly. The strongest base of those examined, NH_2^-, alone catalyzes reactions of the type discussed, although it will probably be found that $(C_6H_5)_2CH^-$ also does so.

Horning (74), in extending these investigations, finds that *p*-phenetidine may be prepared in 31 per cent yield by treating *p*-chlorophenetole with potassium amide in liquid ammonia. Many other aryl halides (such as *p*-chloroanisole, 2-bromopyridine, 2-chloroquinoline, and *p*-chlorophenol at −33°C.) are converted largely to tar under the same conditions. Some halides, possibly because of unfavorable solubility relationships, react only to a slight extent or not at all with potassium amide at −33°C. Among these are *p*-bromobiphenyl, sodium *p*-bromobenzenesulfonate, and *p*-iodobiphenyl.

Somewhat better results were observed in the reaction between the lithium alcoholates of the ammonia system—$LiN(C_2H_5)_2$ and $LiN(n\text{-}C_4H_9)_2$—with aryl chlorides or bromides in ethereal solution. From lithium diethylamide were prepared diethylaniline (60 to 92 per cent), *m*-methyldiethylaminobenzene (23 per cent), and *p*-methyldiethylaminobenzene (35 per cent). From lithium di-*n*-butylamide, di-*n*-butylaniline was made in 36 per cent yield, and from *N*-lithium piperidine, *N*-phenyl piperidine in 47 per cent yield.

VII. ALCOHOLS, PHENOLS, AND ETHERS

Phenols in a mixture have been determined by determining the ammonia evolved when they react with sodium amide (134). Benzohydrol, even with an excess of sodium amide in liquid ammonia, yields only the monosodium salt, $(C_6H_5)_2CHONa$ (90), although Wooster (159a, first reference) states that a dipotassium benzohydrol, $(C_6H_5)_2CK(OK)$, is formed by treating benzohydrol with potassium amide in the same solvent.

Renfrew and Cretcher (123) found that cinchonine and hydroquinine were oxidized to the corresponding ketones, cinchoninone and hydroquininone, by sodium amide in boiling xylene. In attempting to generalize this reaction, it was found that methylisobutylcarbinol was scarcely affected under the same conditions, nor was benzohydrol, except for the formation of an intense purple color (cf. 159a).

According to Mottier (111), sodium amide in tetralin at 200–300°C. splits the monomethyl ethers of pyrocatechol, resorcinol, and hydroquinone into the corresponding phenols in yields of 75 to 100 per cent, the best results being obtained at the higher temperature. The following were not split under the same conditions: the methyl ethers of phenol; the *o*-, *m*-, and *p*-cresols; the dimethyl ethers of pyrocatechol, resorcinol, and hydroquinone; and diphenyl oxide. Sartoretto and Sowa (128a) find that the compound named last is not cleaved by sodium amide in liquid ammonia at −33°C.

Helfer and Mottier (72a) state that in contact with sodium amide methylene pyrocatechol and some of its derivatives (e.g., safrole, dihydrosafrole) are colored blue. The color disappears on heating, and at a sufficiently high temperature a violent reaction occurs with evolution of gas. The corresponding diphenols can be isolated.

The sodium salts of the naphthols are best prepared in liquid ammonia by the action of sodium amide on the naphthol, since reduction products are formed when sodium is used (92).

Mlle. Grédy (57a) has used sodium amide in preparing the methyl ethers of a number of acetylenic alcohols. The following directions are typical: 40 g. of octyne-2-ol-1, $C_5H_{11}C\equiv CCH_2OH$, is converted by sodium amide in absolute ether to the sodium salt, $C_5H_{11}C\equiv CCH_2ONa$, in a rapid reaction. The ether is evaporated to remove ammonia formed in the reaction, and then a solution of 70 g. of dimethyl sulfate in ether is added, the mixture being gently heated for an hour. There is obtained in this manner an 80 per cent yield of the ether, $C_5H_{11}C\equiv CCH_2OCH_3$.

Sodium amide reacts with acetylenic alcohols of the type,

$$C_6H_{11}CH_2C\equiv CC(CH_3)_2OH$$

to form red sodium salts (57b). (C_6H_{11} is cyclohexyl.)

VIII. AMINES

A. *Aliphatic amines*

Glycidic acid, its esters, its amides, or their alkyl, aralkyl, or aryl substitution products are condensed with amines at elevated temperatures under substantially anhydrous conditions, in the manner of the following equation (sodium ethylate or sodium amide may be used as catalysts):

$$R_2\overline{COC}RCOY + R_2NH \rightarrow R_2NC(R_2)C(OH)(R)COY$$

R is hydrogen, alkyl, aryl, or aralkyl. Y is OR or NR_2. With amines containing two reactive amino groups, such as RNH·[ ]·NHR (where[ ] is an alkylene group or CO) products of the formula, $R_2\overline{CNR\cdot[\,]\cdot NRCOC}R(OH)$ are obtained. Thus, β,β-dimethylglycidic acid, its amide or ethyl ester, with aniline or methylaniline and sodium amide give hydroxyanilino (or methylanilino) isovaleric acid, ester, or amide. β,β-Dimethylglycidic acid amide reacts with urea or phenylhydrazine in the presence of sodium amide to form 4,4-dimethyl-2,6-diketo-5-hydroxyhexahydropyrimidine or 1-phenyl-3,3-dimethyl-4-hydroxy-3,4-dihydro-5-pyrazolone, respectively (131).

Fry and Culp (49) have examined the action of fused sodium amide at 250°C. on mono-, di-, and tri-methylamines, and, as with reactions involving the fused alkali hydroxides, find that the following general equation is valid.

$$R(H)_n + nNaNH_2 \rightarrow R(NHNa)_n + nH_2$$

(Cf. $R(H)_n + nNaOH \rightarrow R(ONa)_n + nH_2$.)

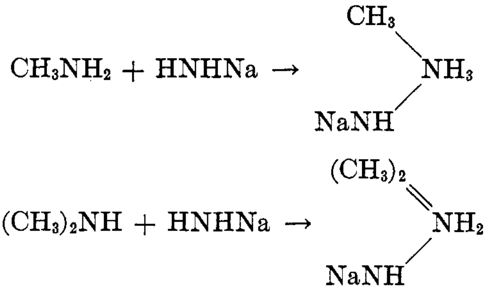
Specifically,

$$CH_3NH_2 + NaNH_2 \rightarrow NaCN + NH_3 + 2H_2$$

$$(CH_3)_2NH + 2NaNH_2 \rightarrow 2NaCN + NH_3 + 4H_2$$

$$(CH_3)_3N + NaNH_2\text{, no reaction}$$

The first two reactions, which take place to the extent of 95 per cent of the theory, are of the nitridation–reduction type, in which hydrogen gas appears in place of an organic reduction product. The methylamines have been nitridized to sodium cyanide. The following mechanism has been tentatively proposed.



$$CH_3NH_2 + HNHNa \rightarrow \begin{matrix} CH_3 \diagdown \\ NH_3 \\ NaNH \diagup \end{matrix}$$

$$(CH_3)_2NH + HNHNa \rightarrow \begin{matrix} (CH_3)_2 \diagdown\!\!\diagdown \\ NH_2 \\ NaNH \diagup \end{matrix}$$

$$(CH_3)_3N + NaNH_2 \rightarrow \text{no addition compound}$$

The intermediate formation of an addition compound of the "ammonium" type is assumed to be necessary before further reaction can occur. Electronic formulas for the above cannot be constructed unless one nitrogen has a decet of electrons.

It may be remarked that trimethylamine is an ether of the ammonia system and that its failure to react with sodium amide is analogous to the failure of aquo ethers to react with heated sodium hydroxide.

B. Aromatic amines[2]

Wohl and Lange (155) used sodium amide to prepare a salt of aniline, which, without isolation, was used to make anilidoacetal, $C_6H_5NHCH_2\text{-}CH(OC_2H_5)_2$.

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[2] See also section I.

Kraus and Bien (90) state that it is impossible to prepare disodium phenylamide, $C_6H_5NNa_2$, by treating monosodium anilide with sodium amide in liquid ammonia. Monosodium anilide and monosodium diphenylamide have been made for conductance measurements in liquid ammonia by the action of sodium amide on aniline and diphenylamine, respectively.

Jones (80a) prepared a metallic derivative of a diarylamine, such as diphenylamine, in liquid ammonia, this solvent being replaced by toluene, and carbon disulfide introduced to give sodium diphenylthiocarbamate.

For the manufacture and use of compounds of the type of sodium diphenylamide, see section XII C (3a).

IX. ALDEHYDES AND ALDEHYDE AMMONIAS

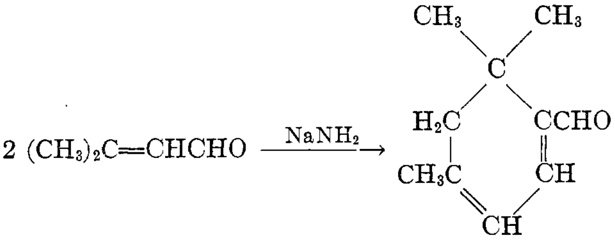
A. *Aliphatic aldehydes, hexamethylenetetramine*

Sodium amide attacks the potassium salt of salicylaldehyde at 250–270°C., but the reaction was not of the Cannizzaro type, in that no salicylic acid was formed. A mixture of potassium hydroxide, sodium hydroxide, and a small amount of sodium amide, however, did react to give salicylic acid (101).

Kirssanov and Ivastchenko (88) suggest that the first step in the reaction between benzaldehyde and sodium amide (in which benzamide and benzyl alcohol are formed) is the addition of the sodium amide to the carbonyl group. Haller (62) has described a compound of the probable structure, $(C_6H_5)_2C(ONa)NH_2$, which was made from sodium amide and benzophenone.

Propionaldehyde, *n*-butyraldehyde, and *n*-heptaldehyde react with liquid ammonia to give viscous liquids, which do not seem to be affected by calcium amide (142).

Fischer and Löwenberg (46) have condensed 2-methylbutenal with a small amount of sodium amide in ether, and have obtained 1,1,5-trimethyl-2-formylcyclohexadiene-2,4 in 50 per cent yield.



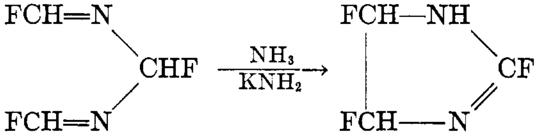
Apparently the presence of a branched-chain methyl in the β-position with respect to the —CHO group is necessary, since crotonaldehyde under similar conditions is converted only to resins. Citral, however, condenses readily in the manner of the above equation to yield a compound, $C_{20}H_{30}O$, which probably contains the same fundamental ring. 1,1,5-Trimethyl-2-formylcyclohexadiene and acetone react in the presence of sodium amide (3–25°C.) with loss of water. (—CHO in the above formula is replaced by $—CH{=}CHCOCH_3$.)

Hexamethylenetetramine, $(CH_2)_6N_4$, does not dissolve in liquid ammonia or in a heated solution of potassium amide in this solvent (142).

X. ALDIMINES, HYDRAMIDES, AND SCHIFF BASES

A. Hydramides

Strain (141) found that hydrofurfuramide (A) slowly dissolves in liquid ammonia to form furine (B), the reaction being greatly accelerated by adding very small quantities of potassium amide.



A B

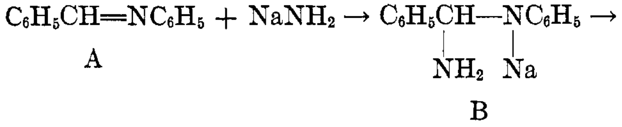
$$C_4H_3O = \alpha\text{-furyl} = F$$

Hydrogen is liberated when furine (B) is treated with an excess of potassium amide in liquid ammonia, but the expected furyl compound corresponding to lophine was not isolated (cf. 6, p. 105).

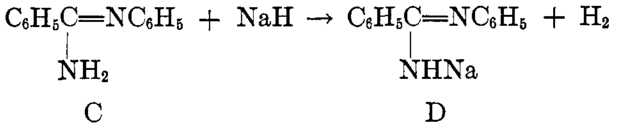
B. Schiff bases

It has previously been found that an excess of potassium amide in liquid ammonia converts benzalaniline, $C_6H_5CH{=}NC_6H_5$, into benzylphenylbenzamidine, $C_6H_5C(NHC_6H_5){=}NCH_2C_6H_5$, in a reaction of the Cannizzaro type (6, p. 105.) Apparently, polymeric Schiff bases result if the potassium amide is used in less than molar proportions.

Altering the experimental conditions, and avoiding the use of liquid ammonia, Kirssanov and Ivastchenko (87, 88) heated a number of Schiff bases with sodium amide under toluene, finding reactions of somewhat greater complexity than in liquid ammonia, as might be expected. Benzalaniline (A) is thus converted to aniline (12 per cent), phenylbenzamidine (C) (20 per cent), benzylaniline (E) (20 per cent), lophine (13 per cent), and some colorless needles, melting at 207–8°C. The reaction is interpreted in the following manner.



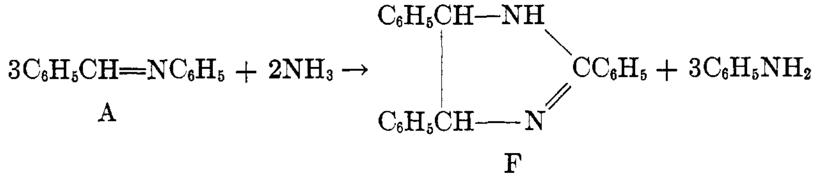
$$\underset{A}{C_6H_5CH{=}NC_6H_5} + NaNH_2 \rightarrow \underset{B}{\underset{NH_2\ \ Na}{C_6H_5CH{-}NC_6H_5}} \rightarrow$$



$$\underset{C}{\underset{NH_2}{C_6H_5C{=}NC_6H_5}} + NaH \rightarrow \underset{D}{\underset{NHNa}{C_6H_5C{=}NC_6H_5}} + H_2$$

$$\underset{A}{C_6H_5CH{=}NC_6H_5} + H_2 \rightarrow \underset{E}{C_6H_5CH_2NHC_6H_5}$$

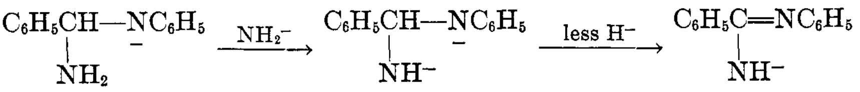
The lophine is probably obtained by the nitridation, or oxidation, of amarine (F), which is known to be formed by the action of alkali amides on hydrobenzamide (6, p. 105). The over-all reaction, expressing the formation of amarine, is the following,



The two hydrogens removed from amarine in forming lophine probably reduce benzalaniline (A → E). No benzylphenylbenzamidine was isolated.

Benzal-*p*-toluidine and sodium amide under the same conditions give tolylbenzamidine (23 per cent), benzyltoluidine (21 per cent), lophine (13 per cent), and *p*-toluidine (13 per cent). Piperonylaniline is only partially attacked in the same length of time.

It will be seen that the interpretation of the reaction mechanism above is modelled after that of Ziegler and Zeiser (168), who have assumed the addition of sodium amide to the —CH=N— bond of pyridine and the loss of sodium hydride from the product to form 2-aminopyridine. The direct conversion of B to D could be brought about in the following manner (the reactions are written ionically):



$$\underset{NH_2}{C_6H_5CH{-}\overset{-}{N}C_6H_5} \xrightarrow{NH_2^-} \underset{NH^-}{C_6H_5CH{-}\overset{-}{N}C_6H_5} \xrightarrow{\text{less } H^-} \underset{NH^-}{C_6H_5C{=}NC_6H_5}$$

H^- (i.e., NaH) is lost because of the influence of the two (−) charges on the hydrogen of the CH group. That is to say, an excess of sodium amide should accelerate the reaction (cf. 5).

If benzylphenylbenzamidine (G) is formed in the reaction, it is doubtless saponified or ammonolyzed by the sodium amide, in some such manner as indicated by the following equations:

$$\underset{\text{G}}{C_6H_5C(NHC_6H_5){=}NCH_2C_6H_5} + NaNH_2 \rightarrow \underset{\text{C}}{C_6H_5C(NHC_6H_5){=}NH} + C_6H_5CH_2NH_2$$

$$\rightarrow \underset{\text{(as sodium salts)}}{C_6H_5C(NH_2){=}NCH_2C_6H_5 + C_6H_5NH_2}$$

Neither benzylamine nor benzylbenzamidine was observed, so they either were not formed or were destroyed by the sodium amide.

From this work, and from an investigation of the formation of amidines from nitriles (section XII F; 29), Kirssanow and his coworkers conclude that the first step in every reaction between sodium amide and a substance containing a —CH=N— or —C≡N linkage is the formation of an addition compound of the type noted (B). Where sodium amide adds to —CH=N— in an open-chain compound or a ring, sodium hydride may be split off in a subsequent reaction, the net result being the conversion of —CH=N— to —C(NH_2)=N—.

XI. KETONES

A. Aliphatic ketones

Isophorone may be prepared by the action of sodium amide on acetone (6, p. 106; 38). Merling, Chrzesciuski, and Pfeffer (107) have patented the formation of the sodium salts of acetone, methyl ethyl ketone, diethyl ketone, cyclopentanone, and methyl propyl ketone by the interaction of sodium amide and the corresponding ketone in ether below −15°C. (see also 6, p. 168, and 27a). These salts are used in the preparation of acetylenic carbinols (section XI C′).

Sodium amide fails to react with liquid ketene (76).

Alkali amides cause citral to condense with acetone and form pseudoionone in better yields, it is claimed, than are obtainable by the usual methods (36).

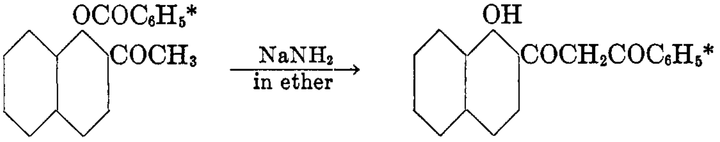
The methylation and ethylation of ketones by means of sodium amide and a methyl or ethyl halide have been extensively investigated by Haller and his coworkers (6, pp. 106–7), but the introduction of higher alkyl radicals appears to have been accomplished in only a few cases. In order to extend this earlier work, Nasarov (113a) has studied the "*n*-propylation" of pinacolone, isobutyrone, and pentamethylacetone, with the result that the following compounds have been prepared: *n*-propylpinacolone, methyl-*n*-propylpinacolone, di-*n*-propylpinacolone, *n*-propylisobutyrone, pentamethyl-*n*-propylacetone, *s*-tetramethyl-di-*n*-propylacetone, *s*-dimethyldiethylacetone, 3,5-dimethyl-3-ethylheptanone-4, and a few others.

Propylation is definitely harder than methylation or ethylation and is best effected by the reaction between *n*-propyl iodide, sodium amide, and the ketone in boiling benzene.

B. Mixed aliphatic-aromatic ketones

s-Dibenzylacetone, when treated with sodium amide and methyl iodide in ether (the process being repeated three times, benzene being used the last two times), gives tetramethyldibenzylacetone (60). Monobenzylacetone could not be successfully alkylated.

Mahal and Venkataraman (103) have discovered the rather peculiar reaction expressed by the equation,

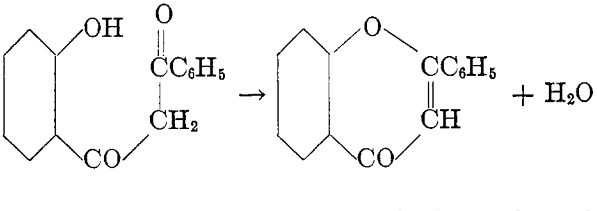


2-Acetyl-1-naphthyl benzoate

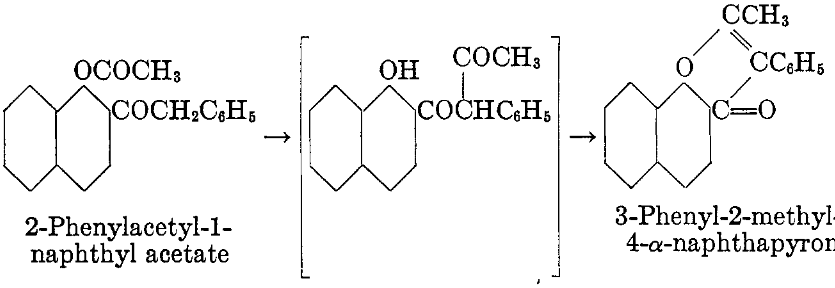
(formed after the reaction product is decomposed by acid)

The phenyl group denoted by an asterisk may contain one, two, or three methoxyl groups.

In continuing this work, Bhalla, Mahal, and Venkataraman (8) treated *o*-benzoyloxyacetophenone, *o*-$C_6H_5COOC_6H_4COCH_3$, with sodium amide in ether and obtained *o*-hydroxydibenzoylmethane, *o*-$HOC_6H_4COCH_2$-COC_6H_5, as one of the reaction products. From this, by the action of sulfuric acid, a pyrone is formed, in accordance with the equation,



It is interesting that in many cases a pyrone is the product of the sodium amide reaction itself. Thus, 1-acetyl-2-naphthyl *o*-methoxybenzoate and 1-acetyl-2-naphthyl *p*-methoxycinnamate provide examples of the partial direct conversion into the pyrone. Substituents in the methyl group of the ketone used in the reaction led chiefly to a pyrone, as in the following example:



2-Phenylacetyl-1-naphthyl acetate

3-Phenyl-2-methyl-1, 4-α-naphthapyrone

Baker (2) has proposed a mechanism for rearrangements of this type.

de Carvallo (15a) has condensed acetophenone with benzophenone and with *p,p'*-dibromobenzophenone in the presence of sodium amide to diphenyldiphenacylmethane, or its dibromo substitution product, in the manner of the equation,

$$(C_6H_5)_2CO + 2CH_3COC_6H_5 \rightarrow H_2O + (C_6H_5)_2C(CH_2COC_6H_5)_2$$

3-Benzoyl-3-methylbutyric acid may be prepared in excellent yield by the reaction of ethyl iodoacetate with the sodium derivative of isopropyl phenyl ketone, $C_6H_5COCNa(CH_3)_2$, with saponification of the ester that is formed first. If ethyl chloroacetate is used instead of ethyl iodoacetate, a glycidic acid, $(CH_3)_2CH\underline{C(C_6H_5)OC}HCOOH$, is formed (70; cf. 6, pp. 113–4).

Sodium amide converts 1,3-dibenzoylpropane in ether to a red disodium derivative, which may be alkylated with methyl iodide to 2,4-dibenzoylpentane. Alkylation of 1,3-dibenzoyl-2-phenylpropane does not give a stable product (3).

C. Cyclic ketones

Sodium amide has been used in the alkylation of benzoylcyclopropane (69).

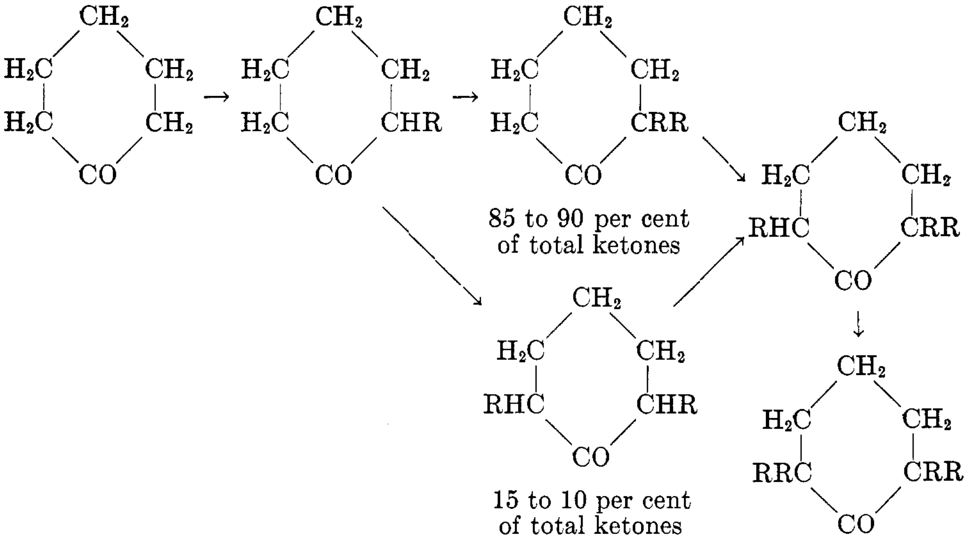
Dimethylindanone is formed by the action of methyl iodide on the reaction product of indanone and sodium amide (68).

Rupe, Bürki, and Werdenberg (127) have used sodium amide in preparing sodium camphor, an intermediate in the synthesis of *d*-, *l*-, and racemic camphorcarboxylic acids. Thiocamphor is changed by sodium amide in ether at 0°C. to a sodium salt, and thence by reaction with amyl nitrite into isonitrosothiocamphor. The latter has been suggested as a reagent for the quantitative estimation of cobalt (135a). The sodium salt of camphor, prepared with the use of sodium amide, is converted to oxymethylenecamphor by amyl formate (126). 4-Methylcamphor and sodium amide react in benzine (b. p. 100°C.) to give a sodium salt, which, with ethyl nitrite, gives methylisonitrosocamphor (113). Oddo (115) has used sodium amide in preparing sodium menthone, from which by carbonation he obtained menthonecarboxylic acid. He claims that the hydrolysis of the reaction product of sodium amide and camphor in toluene (temperature not stated) gives very little camphor, as would be anticipated if salt formation alone had occurred. There were isolated small amounts of dicamphor and dicamphoquinone, a substance melting at 156°C., and a larger quantity of an alkali-insoluble mixture.

In the previous review, a number of articles by Cornubert and his coworkers (30, 31) were inadvertently overlooked, although the references were added on the proof (6, p. 178). These articles are now reviewed below.

1. The alkylation of cyclohexanone

The following scheme expresses the average results obtained in the alkylation of cyclohexanone itself with sodium amide and an alkyl halide in ethereal solution.

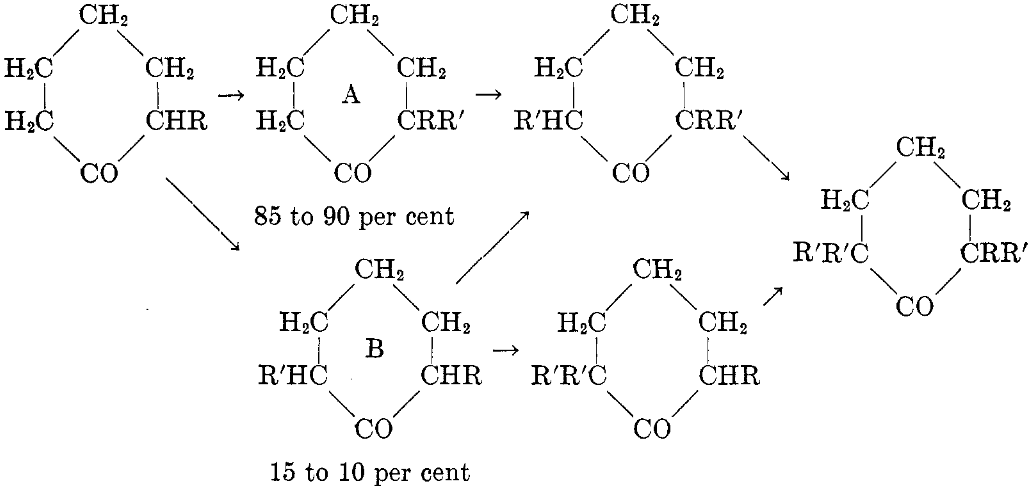


85 to 90 per cent of total ketones

15 to 10 per cent of total ketones

The fixation of one alkyl group is accompanied by that of a second alkyl group in smaller quantity. This reaction is the more important the more concentrated the solution of the ketone. At the same time, the importance of the condensation reaction increases (6, equation 56).

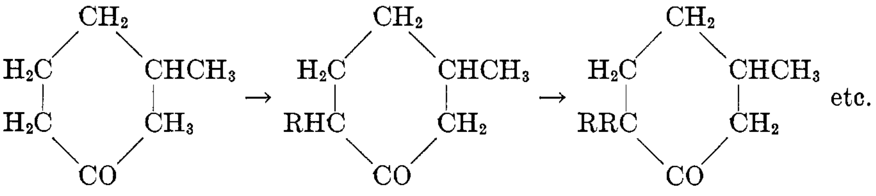
2. The alkylation of α-substituted cyclohexanones



The percentage of the two isomers, A and B, depends to some extent upon the nature of the halogen in the alkyl halide, bromides and iodides giving the same yields, chlorides furnishing mixtures richer in ketone B. The alkyl group preëxisting in the α-position does not always appear to have an influence on the phenomena of orientation. Phenylation and cyclohexylation of α-methylcyclohexanone did not succeed. Isopropylation was effected with poor yield. Steric influences do not appear to have any definite effect.

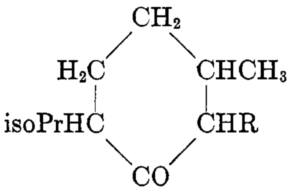
3. Alkylation of β-methylcyclohexanone and of menthone

The alkylation of β-methylcyclohexanone proceeds for the most part in accordance with the following scheme, although minor amounts of the α,α′-dialkyl derivative are formed at the same time.

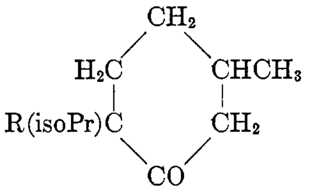


A β-alkyl group therefore has a manifest influence on the position taken by the entering alkyl groups.

Martine (6, p. 173) examined the methylation of menthone and erroneously concluded that the product was chiefly the symmetrical methyl-menthone, formula A below. Cornubert and Humeau (31), however, conclude that the asymmetrical ketone (formula B) is the chief reaction product.

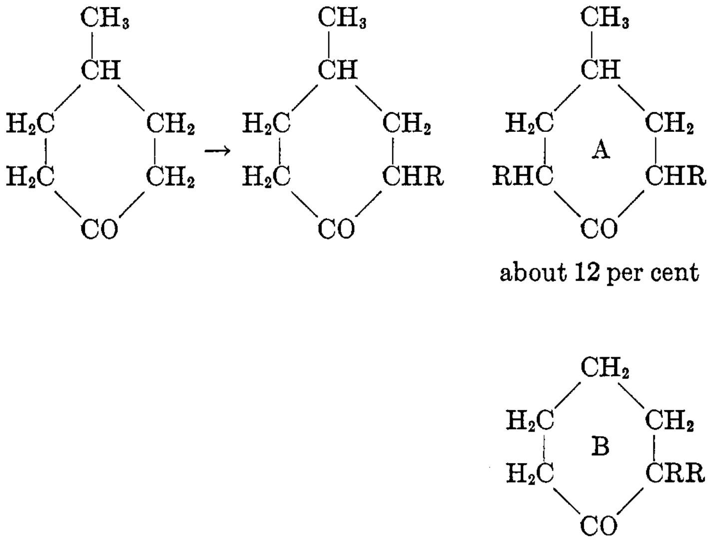


A



B

4. The alkylation of γ-methylcyclohexanone



about 12 per cent

etc.

about 88 per cent

Since the proportion of symmetrical and asymmetrical ketones, A and B, produced in the above reaction is about the same as when cyclohexanone itself is alkylated, the γ-methyl group has no influence on the phenomena of orientation.

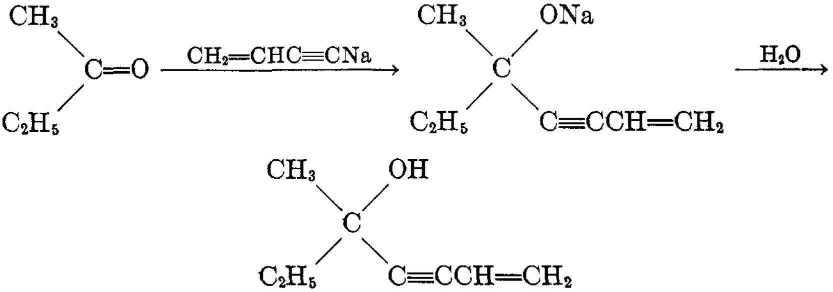
It is shown that the proportion of isomers formed in the alkylation of cyclohexanone or of the three monomethylcyclohexanones is not due to an effect of transposition, such as might be caused by the reagents used in the synthesis.

In the methylation of α-methylcyclopentanone, Haller and Cornubert (6, p. 178) obtained a preponderance of the unsymmetrical α,α-dimethylcyclopentanone, together with a smaller quantity of its α,α′-isomer.

In a later article, entitled "Contribution to a study of the extinction of the ketonic function," Cornubert and his coworkers (32) used sodium amide in preparing tetramethylcyclohexanone, tetraallylcyclohexanone, tetrabenzylcyclohexanone, methylisopropyldiallylcyclohexanone, and triallylmenthone. In the course of the work ketones were found which gave no bisulfite compound, oxime, or semicarbazone, although they could be reduced to the corresponding secondary alcohol.

C′. The preparation of acetylenic carbinols

Methyl ethyl ketone, vinylacetylene, ether, and sodium amide at temperatures of carbon dioxide snow give a 71 per cent yield of vinylethinylmethylethylcarbinol, in accordance with the equation (15),



A patent has been issued for the preparation of the sodium salts of aliphatic ketones, to be used for making acetylenic carbinols (38).

Vinylethinylmethylcarbinol is made in 26 per cent yield by treating the sodium salt of vinylacetylene with acetaldehyde, but in the preparation of this and other secondary carbinols the results were not as good as in the preparation of the tertiary carbinols (15).

D. The scission of ketones by means of sodium amide

Two earlier papers of Haller and Bauer (64, 66) were overlooked in the first review, and are now abstracted.

Trialkylacetamides are prepared by heating trialkylacetophenones, $C_6H_5COCR_3$, in benzene or toluene with sodium amide (6, p. 124). Potassium hydroxide saponifies them with great difficulty, but the corresponding acids may readily be obtained by the action of nitrous acid upon them. There have been prepared the following acid amides, together with the corresponding acids: pivalamide (trimethylacetamide), dimethylethylacetamide, dimethylpropylacetamide, methyldiethylacetamide, dimethylisopropylacetamide, methyldiethylacetamide, triethylacetamide, methylethylpropylacetamide, dimethyllauramide, benzyldimethylacetamide, and others.

Tribenzylmethane, $(C_6H_5CH_2)_3CH$, may be prepared by refluxing ω,ω,ω-tribenzylacetophenone with sodium amide in xylene (73).

Bouveault and Levallois (12a) modified the method of Semmler (6, p. 127) for opening the ring of fenchone with sodium amide.

Chaix and de Rochebouet (16) heated fluorenone with sodium amide in toluene and obtained the amide of biphenyl-*o*-carboxylic acid.

Haller (60) heated tetramethyldibenzylacetone with sodium amide for three days in xylene, obtaining isobutylbenzene and the acid amide, $C_6H_5CH_2C(CH_3)_2CONH_2$. Similarly, $C_6H_5CH_2CH_2COC_2H_5$ gives on alkylation 1-phenyl-2,2,4,4-tetramethyl-3-pentanone, which is decomposed into isobutylbenzene and the amide of trimethylacetic acid. Haller and Bauer heated hexamethylacetone, pentamethylethylacetone, tetramethyldiethylacetone, and triethylpinacolone with sodium amide, obtaining hydrocarbons and trisubstituted acetamides (67a).

G. Ketimines

Benzophenoneimine reacts with sodium amide to form a salt, and with potassium amide to form the salt of an addition compound, in the manner of the following equations (138):

$$(C_6H_5)_2C{=}NH + NaNH_2 \rightarrow (C_6H_5)_2C{=}NNa + NH_3$$

$$(C_6H_5)_2C{=}NH + 2KNH_2 \rightarrow (C_6H_5)_2C(NHK)_2 + NH_3$$

XII. ACIDS AND THEIR DERIVATIVES, EXCLUSIVE OF ESTERS

A. Acids[3]

Wood and Bergstrom (156) have recorded their inability to prepare a dipotassium salt of formic acid ($K{\cdot}COOK$ or $C(OK)_2$) by treating this acid with an excess of potassium amide in liquid ammonia.

B. Acid amides and proteins

The work of Miss Fulton concerning the formation of salts of the acid amides and their decomposition into hydrocarbons by heating with an excess of the reagent has now been published (47a; 6, p. 132). Freer and Sherman (48) previously prepared the sodium salts of formamide and acetamide with the use of sodium amide.

C. The indigo synthesis

Indigo is formed by heating phenylglycinesulfocarboxylic acid with sodium amide at 220°C. (84). α-Phenylhydantoin and its homologues react with heated alkali amides, or with a mixture containing the alkali

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[3] See also section VIII A.

hydroxides in addition, to form a substance (probably indoxyl) which gives indigo on oxidation in air (39).

Belart (3a) has modified the customary process for the production of indigo (6, p. 134) by using organic derivatives of sodium amide in place of sodium amide itself, to cyclize phenylglycine-*o*-carboxylic acid. The sodium derivatives of aniline, naphthylamine, diphenylamine, tolylamine, and xylylamine have been specifically mentioned.

D. The preparation of substituted indoles

Julian and Pikl (81) used the method of Verley and Beduwé (150) to prepare *n*-propylindole.

E. Acid chlorides

Carbonyl chloride has been treated previously (see pp. 422, 431) (118, 119).

F. Nitriles and related compounds

1. The alkylation of nitriles

Ziegler and Ohlinger (167; 6, pp. 136–7) found that secondary aliphatic nitriles react with lithium diethylamide and similar metallic alcoholates of the ammonia system to form salts which could be alkylated, as shown by the following equations:

$$(CH_3)_2CHCN + LiN(C_2H_5)_2 \rightarrow (C_2H_5)_2NH + (CH_3)_2C(Li)CN$$

$$(CH_3)_2C(Li)CN + CH_2{=}CHCH_2Cl \rightarrow LiCl + (C_2H_5)_2C(CN)CH_2CH{=}CH_2$$

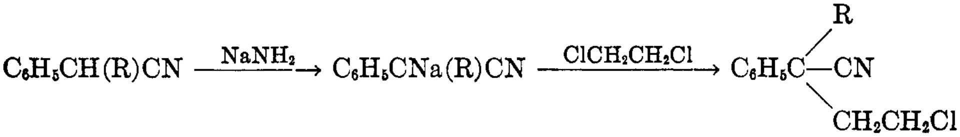
In attempting to extend this reaction to the preparation of salts of the primary nitriles, such as acetonitrile, it was found that large amounts of the lithium derivatives of the dimeric nitriles were formed, particularly if the ratio of nitrile to lithium dialkylamide were 2 to 1.

$$RCH_2CN + RCH(Li)CN \rightarrow RCH_2C({=}NLi)CH(R)CN$$

The reaction is analogous to the formation of ketimides when nitriles are treated with the Grignard reagent. As an example, acetonitrile, added to a solution of lithium diethylamide in ether at -10°C., gives a 78 per cent yield of the dimeric nitrile. Similarly, *n*-butyronitrile gives 71.5 per cent of the dimer, α-butyrylbutyronitrile, but a 90 per cent yield is obtained when lithium ethylanilide is used as the condensing agent (166).

Many patents have been issued to Ziegler for the preparation of substituted nitriles, and their conversion to acid amides of possible medicinal value (162). One such patent (162b) states that secondary nitriles of the general formula, R_2CHCN, in which R represents alkyl (except vinyl) or aralkyl groups, are treated with alkali metal, magnesium, or halogen magnesium substitution products of secondary aliphatic or hydroaromatic amides to form metal derivatives, these then being treated with halogen alkylene compounds or with dialkyl sulfates. Thus, diallylacetonitrile is treated with dicyclohexylamine and $(C_2H_4Br)_2Mg$ solution ($\rightarrow (C_6H_{11})_2NMgBr$), a —MgBr derivative of the nitrile being formed. The —MgBr group is replaced by allyl on treatment with allyl bromide, to give triallylacetonitrile.

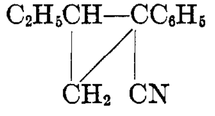
Hastings and Cloke (71) prepared several α-phenyl-α-alkyl-γ-chlorobutyronitriles by the method of Bodroux and Taboury (6, pp. 138–40), and as shown by the following equations (R = alkyl):



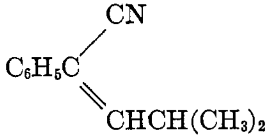
$$C_6H_5CH(R)CN \xrightarrow{NaNH_2} C_6H_5CNa(R)CN \xrightarrow{ClCH_2CH_2Cl} C_6H_5\overset{R}{\underset{CH_2CH_2Cl}{C}}—CN$$

Ethylene chlorohydrin can be used in this synthesis, the hydroxyl group of the resulting condensation product being replaced with chlorine, but the method represented by the equation is recommended. The alkylphenylbutyronitriles form pyrrolines by the method of Cloke (25a).

Murray and Cloke (111a) record the preparation of 1-phenyl-2-ethylcyclopropanecarbonitrile (A), α-phenyl-β-ethylacrylonitrile, α-phenyl-β-isopropylacrylonitrile (B), and some of their derivatives by the general method of a previous article (cf. 6, p. 140).



A



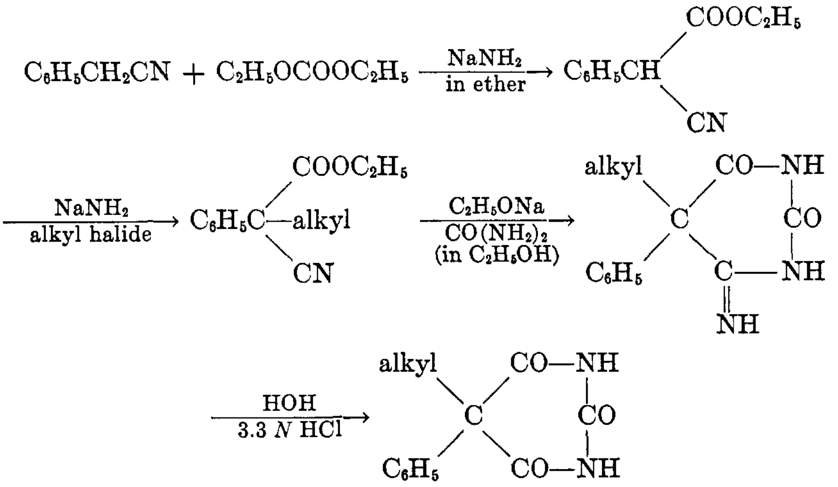
B

The formation of B by the condensation of 1,2-dichloroisobutane and phenylacetonitrile with sodium amide involves a rearrangement, possibly from the β,γ-unsaturated nitrile (C), which would result from the reaction,

$$C_6H_5CHNaCN + (CH_3)_2CClCH_2Cl \rightarrow C_6H_5CH(CN)CH_2CCl(CH_3)_2$$

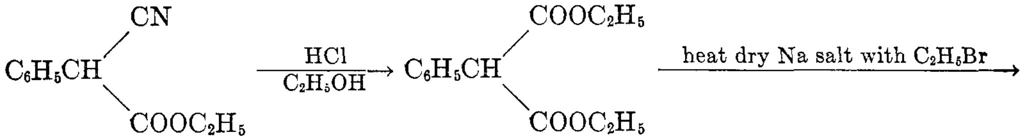
$$\xrightarrow{-\ HCl} \underset{C}{C_6H_5CH(CN)CH{=}C(CH_3)_2}$$

Chamberlain, Chap, Doyle, and Spaulding (17) have prepared the following 5,5-alkylphenylbarbituric acids from intermediates made with the use of sodium amide: ethyl-, isopropyl-, isoamyl-, *n*-hexyl-, and *n*-heptyl. A typical reaction is expressed by the following equations:



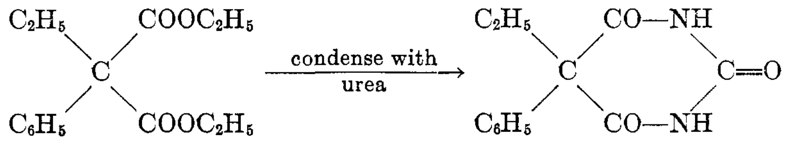
It was noted that the condensation of phenylacetonitrile with diethyl carbonate is best effected by using sodium amide in absolutely anhydrous ether, with continued refluxing and stirring. A by-product results from the probable reaction of two moles of the nitrile with one of the carbonate, its formation being favored by non-anhydrous conditions and too long refluxing. Alkylation of the cyanophenylacetate and the condensation of the resulting compound with urea takes place in absolute alcohol in the presence of sodium amide or sodium ethylate, the product, a 5,5-alkylphenyl-4-iminobarbituric acid being hydrolyzed to a 5,5-alkylphenylbarbituric acid.

Nelson and Cretcher (114) had previously used the method just described to prepare ethyl phenylcyanoacetate (A), which was converted to luminal in accordance with the scheme,



(in 70 per cent yield)

A



Luminal

Phenylvinyloxyethylacetonitrile, $C_6H_5CH(CH_2CH_2OCH{=}CH_2)CN$, was prepared from phenylacetonitrile, β-chloroethyl vinyl ether, and sodium amide.

Kaufmann, Dändliker, and Burkhardt (86) made the sodium salt of phenylacetonitrile in ether with the use of sodium amide, and then added ethyl quinaldate, obtaining cyanobenzyl quinolyl ketone, $C_9H_6NCOCH(CN)C_6H_5$. When this is saponified (with sulfuric acid) an acid is formed, which loses carbon dioxide, giving benzyl 2-quinolyl ketone.

γ-Chlorobutyronitrile and sodium amide react to give cyclopropanecarboxylic acid amide in poor yield (100).

Dolique (35a) prepared α-phenylhexonitrile from phenylacetonitrile, sodium amide, and *n*-butyl bromide.

2. The formation of salts of the amidines

Concentrated solutions of the potassium salts of the lower aliphatic acid amidines in liquid ammonia conduct the current readily, and at high current densities give a mixture of saturated hydrocarbon gases at the anode (50). Salts of the amidines are of course readily prepared by adding a nitrile to a solution of potassium amide in liquid ammonia (29). Only in the case of acetamidine did the anodic reaction go in the anticipated manner, that is, in the sense of the equation,

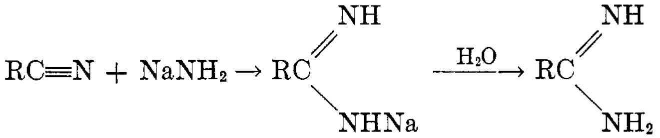
$$2RC({=}NH)NH^- \rightarrow 2CNNH_2 + RR$$

$$(CNNH_2 + 2NH_2^- \rightarrow CNN^{--} + 2NH_3)$$

In all other cases, the hydrocarbons obtained were chiefly mixtures of methane and ethane, which presumably resulted from some kind of thermal decomposition at the electrode. Insofar as the formation of ethane and the ammonocarbonic acid, cyanamide (as a potassium salt), is concerned, this reaction is analogous to the well-known Kolbe synthesis, in which ethane and an aquocarbonic acid salt (potassium carbonate) are formed anodically when a concentrated aqueous solution of potassium acetate is electrolyzed.

Ziegler (164) has patented the preparation of acid amidines containing at least four carbon atoms by treating the nitrile with sodium amide (in the absence of liquid ammonia) at a temperature below the decomposition temperature of the resulting sodium salt of the amidine. The latter is formed on hydrolysis.

Kirssanov and Poliakova (89) studied the action of sodium amide on aromatic nitriles, and found that unsubstituted amidines were always obtained, in accordance with the equation,



$$RC{\equiv}N + NaNH_2 \rightarrow RC(=NH)NHNa \xrightarrow{H_2O} RC(=NH)NH_2$$

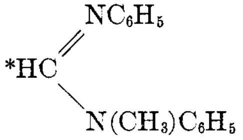
Only small yields of amidine were obtained by heating the aryl cyanide with sodium amide alone, but in the presence of a diluent (boiling toluene, six hours) the following yields have been obtained: benzamidine from benzonitrile, 15 to 20 per cent; *p*-toluamidine from *p*-tolunitrile, 60 per cent; and β-naphthoamidine from β-naphthonitrile, 40 to 50 per cent.

The action of sodium amide on nitriles and on Schiff bases is similar, since in the first stage the reagent always adds to a multiple bond between carbon and nitrogen.

Acetonitrile reacts violently with an excess of sodium amide in ether, but in spite of numerous variations in the conditions under which the reaction was carried out, it was impossible to isolate acetamidine. The velocity of polymerization (dimerization, probably) appears to be more rapid than the velocity of formation of the amidine.

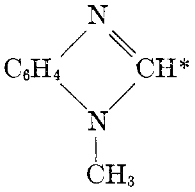
The claim is made that the crystalline compounds obtained by Cornell (29) when metallic amides in liquid ammonia react with nitriles are probably not the salts of amidines, but are double compounds of the nitriles with the amidines. Cornell's analyses, however, seem to indicate quite definitely that salts of the type, $RC(=NH)NHM$, are formed (M is a univalent metal).

Diphenylmethylformamidine



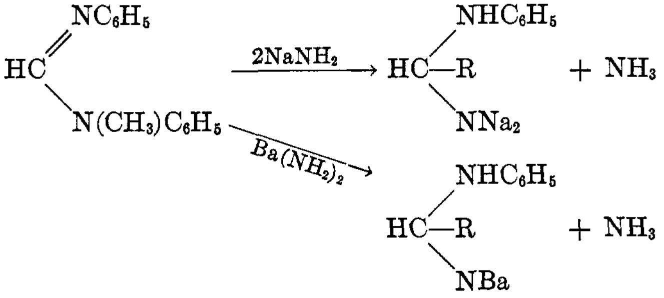
$$^{*}HC(=NC_6H_5)N(CH_3)C_6H_5$$

and *N*-methylbenzimidazole

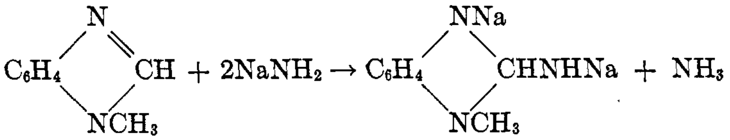


may be regarded as substituted amidines, and therefore as related to the nitriles, or as neutral esters of ammonoformic acid, or formamidine. Unsuccessful attempts were made by Wood (156) to show that the hydrogen atoms designated by asterisks were acidic and capable of replacement with an alkali metal. Such metallic salts it was hoped would clearly show the reactions of compounds containing "divalent" carbon.

However, it was found that both alkali and alkaline-earth amides added to the double bond between carbon and nitrogen to give substances that might be regarded as salts of ammonoörthoformic esters. Thus,



$R = —N(CH_3)C_6H_5$

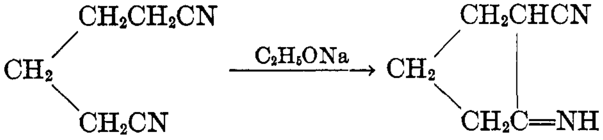


(approximately)

The assumed structure of these salts has not been definitely proven.

3. The use of aliphatic dinitriles in the preparation of large-ring systems

Thorpe (145), in 1909, treated adiponitrile with sodium ethylate and obtained 1-imino-2-cyanocyclopentane, in accordance with the equation:



The synthesis of larger rings by this process always gave unsatisfactory yields, until Ziegler, Eberle, and Ohlinger (166) discovered that metallic derivatives of the primary and secondary alkyl or aralkyl amines were excellent condensing agents. Unfortunately, their use involves several experimental difficulties. The tendency of a dinitrile to dimerize, in the manner of the equation,

$$RCH_2CN + RCHLiCN \rightarrow \underset{\displaystyle RCHCN}{RCH_2C{=}NLi}$$

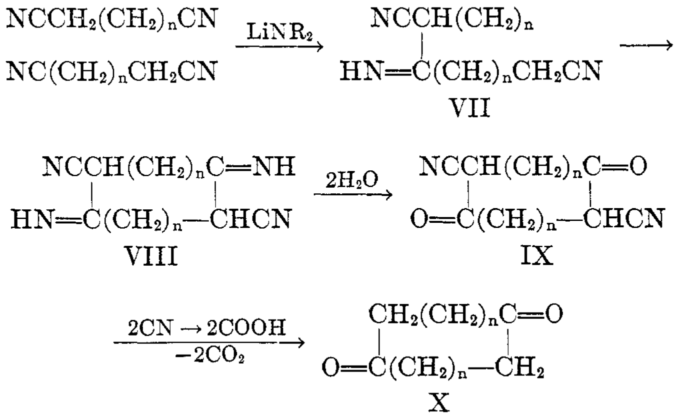
must be overcome, and the formation of a dilithium (or dimetallic) salt of a nitrile must be prevented, since it is only the monolithium salt that readily undergoes cyclization. (Reactions of the type,

$$\mathrm{RCH_2CN + (C_2H_5)_2NLi \rightarrow R_2C(Li)CN + (C_2H_5)_2NH}$$

are practically irreversible under the conditions used.) The reaction of dinitriles with substituted alkali metal amides to give five- and six-membered ring compounds occurs readily in spite of fairly high concentrations of the condensing agent, but the larger rings can be made only by adding the nitrile very slowly to a solution of the condensing agent in a large volume of ether, in order to keep the nitrile concentration below the point at which unwanted side reactions predominate. The following examples will illustrate:

(*1*) An ethereal solution of lithium diethylamide, $\mathrm{(C_2H_5)_2NLi}$, (0.8 *N*) was added to sebacic dinitrile, $\mathrm{CN(CH_2)_8CN}$, in the same solvent, a 13 per cent yield of cyanocycloheptanone being isolated after hydrolysis. (The imino group in the primary product has been replaced by oxygen.)

(*2*) The following procedure gave much better results: 1,14-Dicyanotetradecane (50 g.) was added with stirring to a solution of lithium phenylethylamide (from 93 g. of ethylaniline and an equivalent of lithium *n*-butyl) in 3 liters of ether during 14 × 24 hours. On standing the ethereal solution deposited 7 g. of a diketimide (formula VIII, n = 13, a 30-membered ring). After evaporation of the solvent ether there was obtained a residue (34 g.), from the hydrolysate of which cyclopentadecanone (16.6 g., or a yield of 37 per cent) and a diketone (thirty carbon atoms in the ring) were isolated. Some of the reactions that occur in this synthesis are expressed in generalized terms below.

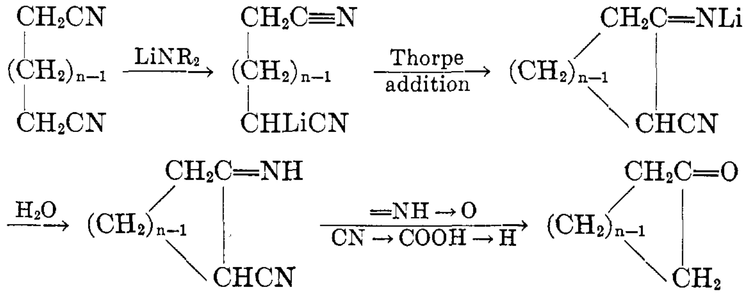


$$\begin{array}{c}\mathrm{NCCH_2(CH_2)_nCN}\\ \mathrm{NC(CH_2)_nCH_2CN}\end{array} \xrightarrow{\mathrm{LiNR_2}} \underset{\text{VII}}{\begin{array}{l}\mathrm{NCCH(CH_2)_n}\\ \quad\;|\\ \mathrm{HN{=}C(CH_2)_nCH_2CN}\end{array}} \longrightarrow$$

$$\underset{\text{VIII}}{\begin{array}{l}\mathrm{\quad NCCH(CH_2)_nC{=}NH}\\ \qquad\;|\qquad\quad\;\;|\\ \mathrm{HN{=}C(CH_2)_n{-}CHCN}\end{array}} \xrightarrow{\mathrm{2H_2O}} \underset{\text{IX}}{\begin{array}{l}\mathrm{\;NCCH(CH_2)_nC{=}O}\\ \qquad|\qquad\quad\;\;|\\ \mathrm{O{=}C(CH_2)_n{-}CHCN}\end{array}}$$

$$\xrightarrow[\mathrm{-2CO_2}]{\mathrm{2CN \rightarrow 2COOH}} \underset{\text{X}}{\begin{array}{l}\mathrm{\quad CH_2(CH_2)_nC{=}O}\\ \qquad|\qquad\quad\;\;|\\ \mathrm{O{=}C(CH_2)_n{-}CH_2}\end{array}}$$

and



XI XII

(*3*) From 55 g. of 1,16-dicyanohexadecane, under the conditions of the above experiment, there were obtained 26 g. of dihydrocivetone (formula XII, n = 15) and 9 g. of tetratriacontadione (formula X, n = 15), among other products. The total yield of cyclic materials was 70 per cent of the theoretical.

Since this article was published, there have appeared a large number of patents dealing with the preparation of cyclic compounds containing large rings, essentially by the methods outlined above, but with some modifications (163). The following is representative (163a): Nitriles having the general formula, $NC(CH_2)_nCN$, can be condensed to form cyclic α-cyanoketimides having the formula, $HN{=}\overline{C(CH_2)_{n-1}C}HCN$, by acting upon them with a condensing agent of the type $(R'R''N)M$, where R′ and R″ may be alkyl, aralkyl, aryl, or alicyclic radicals, while M may be an alkali metal, such as sodium or lithium, an alkaline-earth metal, as magnesium, or other metals, such as aluminum or the rare earths. At the same time, two moles will combine to form cyclic diimine dinitriles.

In the case of cyclic systems comprising five or six links, the reaction occurs smoothly without any particular degree of dilution being required. When preparing cyclic compounds containing more than six links, it has been found preferable to operate with a high degree of dilution. Operation at low concentrations is important when producing cyclic systems composed of more than seven links. By saponification, the α-cyanoketimines can be converted to α-cyanoketones. These compounds may be used in organic syntheses, or for the preparation of scents.

4. Cyanogen

Perret and Perrot (118) have examined the action of sodium amide on cyanogen, and find that the first reaction is expressed by the equation (cf. 29),

$$2NaNH_2 + C_2N_2 \rightarrow Na_2CN_2 + NH_4CN$$

That is to say, an anammonide of an ammonoöxalic acid is split by an ammono base, sodium amide, to salts of an ammonocarbonic and an ammonocarbonous acid. (It is assumed that ammonium cyanide will react further with sodium amide to form sodium cyanide and ammonia.) Dicyanimide, $(NC)_2NH$, is not formed, since it reacts with sodium amide in the following manner:

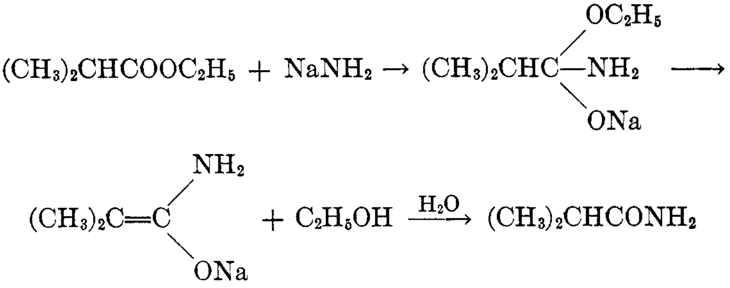
$$3NaNH_2 + (NC)_2CNa \rightarrow 2Na_2CN_2 + 2NH_3$$

Franklin (47b) has previously found that all ammonocarbonic acids—including, of course, dicyanimide—react with heated sodium amide to give disodium cyanamide, Na_2CN_2.

XIII. ESTERS[4]

Wood (156) records the failure to prepare potassium ethyl carbonite, $C(OC_2H_5)OK$, by treating ethyl formate with potassium amide in liquid ammonia. The ester appears merely to be saponified.

Ethyl chloroformate, added to the product of the reaction of sodium amide and ethyl isobutyrate in ether, gives a mixture from whose hydrolysate may be isolated unused ethyl isobutyrate, ethyl carbonate, isobutyramide (the chief product), and diisobutyramide. Certainly the last two would be obtained even in the absence of ethyl chloroformate. The following interpretation is given.



$$(CH_3)_2CHCOOC_2H_5 + NaNH_2 \rightarrow (CH_3)_2CHC\begin{cases} OC_2H_5 \\ NH_2 \\ ONa \end{cases} \longrightarrow$$

$$(CH_3)_2C{=}C\begin{cases} NH_2 \\ ONa \end{cases} + C_2H_5OH \xrightarrow{H_2O} (CH_3)_2CHCONH_2$$

Sodium amide is inferior to sodium ethylate as a condensing agent in the reaction of diethyl malonic ester and urea to form diethylbarbituric acid (45).

Tingle and Gorsline (146) claim that sodium amide is almost useless in effecting Claisen condensations with camphor as the ketone.

Diethyl terephthalate and acetone are condensed by sodium amide in ether to terephthalyldiacetone (3b). Lux (102) finds that sodium amide in ether effects a condensation between ethyl carbonate and acetone to

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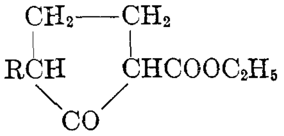
[4] See also section XII, p. 455, concerning *N*-methylbenzimidazole and diphenylmethylformamidine.

form acetoacetic ester, the yield (30 per cent), however, being inferior to experiments in which metallic sodium was used (38 to 41 per cent).

Haller and Cornubert (69a) have improved the method of Bouveault and Locquin (6, p. 147) for the preparation of ethyl cyclopentanonecarboxylate,



(yield, 70 to 80 per cent) by cyclization of ethyl adipate, $C_2H_5OCO(CH_2)_4COOC_2H_5$, with sodium amide. This is a Dieckmann reaction. ($R = H$.) The corresponding α-methyl derivative ($R = CH_3$) was made from ethyl α-methyladipate.

The work of Griswold (6, p. 146) concerning the action of potassium amide in liquid ammonia on the dialkylcyanamides (i.e., esters of an ammonocarbonic acid, cyanamide) has been published since the first review (47).

Diethoxyacetic ester, $(C_2H_5O)_2CHCOOC_2H_5$, and sodium amide react in ether to give the sodium salt of diethoxyacetamide (129) (saponification).

Schwarz and Giese (135) state that ethyl and amyl nitrites fail to react with liquid ammonia at low temperatures, although a vigorous reaction occurs with a solution of potassium amide, in the manner, essentially, of the equation,

$$2C_5H_{11}ONO + KNH_2 \rightarrow (C_5H_{11})_2O + KNO_2 + N_2 + H_2O$$

XIV. ORGANIC DERIVATIVES OF HYDROXYLAMINE AND HYDRAZINE

Kraus and Bien (90) prepared disodium benzhydrazide, $C_6H_5NNa\cdot NNaC_6H_5$, for conductivity work by treating hydrazobenzene with sodium amide in liquid ammonia, but they were unable to make the monosodium salt.

Hauser and Jordan (72), in connection with an investigation of the action of alkalis on acetyl-α- and β-benzaldoximes have found that the former are converted to potassium salts of the oxime and acetamide, or to nitriles, potassium acetate, and ammonia, in accordance with the equations,

$$\underset{\alpha}{RCH{=}NOCOCH_3} + KNH_2 \begin{cases} \xrightarrow{\text{chiefly}} RCN + CH_3COOK + NH_3 \\ \longrightarrow RCH{=}NOK + CH_3CONH_2 \end{cases}$$

R is a substituted phenyl group. When R is 4-methoxyphenyl, 47 per cent of the theoretical quantity of the nitrile, a trace of acetic acid, and 43 per cent of the oxime are formed; when R is 2-chlorophenyl, the yields are 80 per cent of the nitrile and 9 per cent of the oxime; and when R is 3-nitrophenyl, there is obtained 23 per cent of the nitrile, 60 per cent of a gum, and 8 per cent of the oxime. From this, and other work not reported here, it is concluded that α- and β-aldoxime acetates undergo fundamentally the same type of reaction with alkali, but differ primarily in the ease with which they eliminate acetic acid, the β-isomers undergoing this reaction more readily.

XV. NITRO AND NITROSO COMPOUNDS

Diphenylnitrosamine in liquid ammonia solution reacts with the amides of lithium, sodium, potassium, and calcium in accordance with the equation,

$$R_2NNO + MNH_2 \rightarrow R_2NH + MOH + N_2$$

For simplicity, M is an univalent alkali metal.

p-Tolylnitrosamine reacts similarly with sodium amide and potassium amide, but dibenzylnitrosamine and methylphenylnitrosamine do not react in the manner of the above equation. In these reactions no direct evidence was found for the formation of the salt, $NO \cdot NHK$ (44).

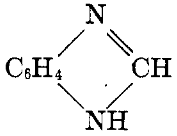
Buehler (14), in continuing the preliminary work of Williams and Bergstrom (6, pp. 151–2), has found that nitrobenzene reacts with sodium amide in liquid ammonia (−33°C.) with the evolution of some nitrogen. There is practically no further formation of gas after standing for half a day, indicating that the dissolved substance has a fair stability. If β-naphthol is added at this stage, or if the initial reaction is carried out in the presence of β-naphthol, there results the dye, phenylazo-β-naphthol, $C_6H_5N{=}NC_{10}H_6OH$-β. The yields depend upon experimental conditions and are as high as 33 per cent. Sodium amide must be in excess of two equivalents for the best results. Dye formation was observed when the following nitro compounds were treated with sodium amide in the presence of β-naphthol: *p*-nitrotoluene, 4-nitrobiphenyl, *o*-nitrobenzoic acid, *o*-nitrotoluene, and 4,4′-dinitrobiphenyl. The above reactions, whose significance will be discussed later, follow the equation,

$$C_6H_5NO_2 + 2NaNH_2 \rightarrow \underset{\text{A}}{C_6H_5N{=}NONa} + NaOH + NH_3$$

Compound A must be sodium normal benzene diazotate, since the isodiazotate does not couple with β-naphthol in ammonia.

XVI. FIVE-MEMBERED HETEROCYCLIC RING SYSTEMS[5]

With the use of the metallic amides, only one hydrogen atom of benzimidazole,



can be replaced by potassium, lithium, or barium in liquid ammonia, in agreement with the accepted formula above. (The lithium and barium salts retain ammonia of crystallization.) It has thus proven impossible to prepare nitrogen analogues of the hypothetical dipotassium aquocarbonite, $C(OK)_2$ (156).

Sodium indole may be prepared by introducing sodium amide into molten indole at 120–160°C. (153).

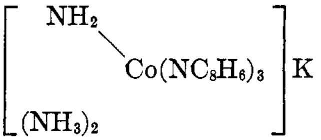
Schmitz-Dumont and St. Pateras (134a) have prepared several coordination compounds of potassium pyrrole and potassium indole in liquid ammonia, in the general manner represented by the equations,

$$\underset{A}{4(C_4H_4N)K} + \underset{B}{Fe(NH_3)_6Cl_2} \xrightarrow{\text{liquid } NH_3} \underset{C}{[(C_4H_4N)_4Fe]K_2} + \underset{D}{2KCl} + 6NH_3$$

Potassium pyrrole (A) is very soluble in liquid ammonia, as is the coordination compound (C), while B and D have very low solubilities.

$$\underset{\text{Potassium indole}}{4(C_8H_6N)K} + Ni(NH_3)_6SO_4 = K_2SO_4 + 6NH_3 + [(C_8H_6N)_4Ni]K_2$$

A double salt of the composition,



$$\left[\begin{matrix} NH_2 & \\ & Co(NC_8H_6)_3 \\ (NH_3)_2 & \end{matrix}\right]K$$

is formed from potassium indole and chloropentamminochromium chloride in liquid ammonia. A more complex salt of this nature was prepared from potassium indole and hexamminocobaltic chloride.

γ-Butyrolactone does not react with sodium amide in ether (107a).

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[5] The reaction of *N*-methylbenzimidazole with the alkali and alkaline-earth amides is described under section XII F.

2-Methylfurane does not react with sodium amide at temperatures between 60°C. and 100°C. (53).

XVII. SIX-MEMBERED HETEROCYCLIC RING SYSTEMS

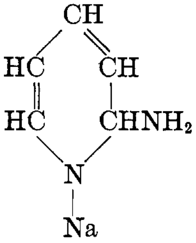
A. Pyridine and its derivatives

According to Goost and Lommel (55), pyridine and its homologues are refined by treatment with a compound containing the group $=N \cdot M$ or $—N \cdot M$, where M is an alkali or alkaline-earth metal. Thus, commercial pyridine may be heated to 110°C. with 5 per cent of disodium cyanamide, Na_2CN_2, or stirred at ordinary temperature with 3 to 5 per cent of sodium amide. This treatment is particularly useful, it is claimed, as a preliminary to catalytic hydrogenations.

The synthesis of 2-aminopyridine, by the action of sodium amide on pyridine in heated indifferent solvents, has been known since the work of Chichibabin and Seide in 1914 (25), but has since been the subject of occasional patents. Thus, an 80 per cent yield is claimed in a German patent (35), if equimolar proportions of sodium amide and pyridine are brought into reaction in a medium such as toluene, at temperatures that are preferably under 100°C. It has been the experience of many that a yield of 50 to 60 per cent is all that can be expected (cf. 154). Shreve (136) has used a steel ball mill for the preparation of sodium amide, and for a reaction vessel in which the synthesis of 2-aminopyridine and 2,6-diaminopyridine is carried out. 2-Aminopyridine, 2,6-diaminopyridine, and 2,4-diaminopyridine have been obtained by heating a suspension of sodium amide in dimethylaniline with pyridine (116). With sodium amide 2-aminopyridine forms a sodium salt, which can be alkylated with methyl iodide (24).

Chichibabin (20) has prepared 2,6-dimethyl-4-aminopyridine by heating 2,6-dimethylpyridine with sodium amide in toluene for twenty-two hours. A German patent (19) relates to the preparation of aminated pyridine homologues in the presence of high-boiling indifferent solvents (xylene, cumene, mesitylene, etc.) at temperatures over 150°C., using either sodium amide or metallic sodium and gaseous ammonia. 6-Amino-2-methyl-5-ethylpyridine and 2-amino-4-ethylpyridine have been described, among others. Schneiderwirth (133) has heated a mixture of 2-alkylpyridine with sodium amide to a temperature of not less than 200°C., obtaining 4,6-diamino-2-alkylpyridines, such as 4,6-diamino-2-methylpyridine and 4,6-diamino-2-propylpyridine.

Feist and coworkers (43) prepared 2-aminopyridine by a modified Chichibabin method, which is claimed to be an improvement. The mechanism of the formation of 2-aminopyridine has been extensively discussed by Kirssanov and Ivastchenko (88) and by Kirssanov and Poliakova (89) (see section X), who conclude that an addition compound,



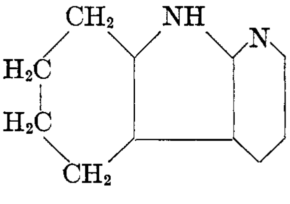
is the first reaction product, in accordance with an earlier suggestion of Ziegler and Zeiser (168). On heating this loses sodium hydride to give 2-aminopyridine, which is subsequently converted by the liberated sodium hydride to a sodium salt. Support for this view was obtained as a result of the study of reactions of the type,

$$C_6H_5CH{=}NC_6H_5 + NaNH_2 \rightarrow C_6H_5C(NHNa){=}NC_6H_5 + H_2$$

$$C_6H_5CN + NaNH_2 \rightarrow C_6H_5C({=}NH)NHNa$$

The mechanism of this reaction has also been discussed by Kabachnik (82), who likewise favors Ziegler's scheme (168) for the formation of 2-aminopyridine. Dipyridyls accompany amino derivatives in all cases, and sometimes predominate in the more complex compounds, as is the case with 2,5-dimethylpyrazine (6, p. 161). Their formation is due to the replacement of an α- or γ-hydrogen of the pyridine base with sodium, ammonia being evolved. The sodium compound then adds to the double bond between carbon and nitrogen of another molecule of the heterocyclic base, just as does sodium amide, to give a dihydro derivative, which is oxidized to the dipyridyl.

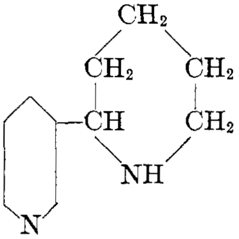
2-Aminopyridine condenses with *o*-chlorocyclohexanone and sodium amide in toluene (78) to



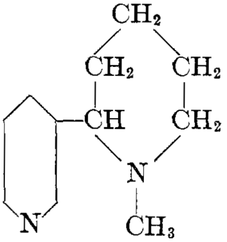
3-Hydroxypyridine in methanol and sodium amide in *p*-cymene when heated together give 2,6-diaminopyridine, the hydroxyl having been replaced by hydrogen (121).

Tjeen Willink, Jr., and Wibaut (147) find that 2,2′-dipyridyl is only slightly attacked by sodium amide in boiling toluene (fourteen hours) with the apparent formation of a small amount of a diaminodipyridyl, m.p. 185–6°C. (Boiling xylene gives better results.) 2,2′-Diamino-4,4′-dipyridyl may be formed more readily (19). A monoamino-2,2′-dipyridyl may be prepared by treating 2,2′-dipyridyl with an excess of potassium amide and potassium nitrate in liquid ammonia at room temperatures (m.p. of product, 135.5–6.5°C.) (7a).

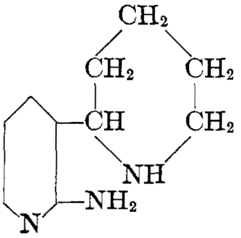
Several articles (83, 85, 106) have appeared dealing with the amination of anabasine,



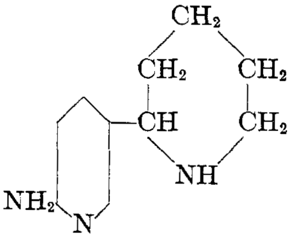
and *N*-methylanabasine,



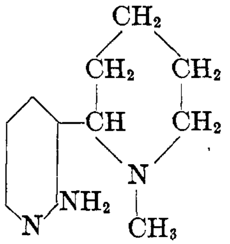
The reactions were best carried out with sodium amide in dimethylaniline at a temperature of 120–150°C., since yields of about 40 per cent were obtained, as against the 5 per cent yield reported by Menschikov, Grigorovitch, and Orechoff (106) in boiling xylene. *N*-methylanabasine was however aminated in this solvent to two isomeric amino-*N*-methylanabasines, which are formed in a total yield of 45 to 50 per cent (106). The following compounds have been prepared:



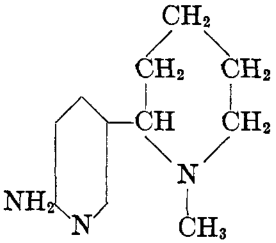
α-Aminoanabasine
m.p. 89.5–90°C.



α′-Aminoanabasine
m.p. 109°C.

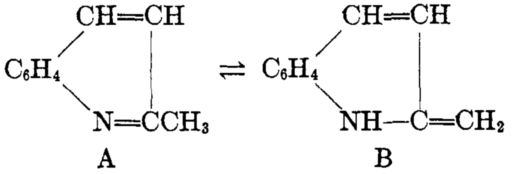


α-Amino-*N*-methylanabasine
m.p. 95°C.

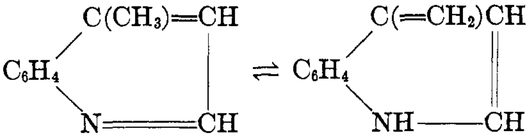


α′-Amino-*N*-methylanabasine
oil

Some years ago, Chichibabin (21) suggested that the 2- and 4-methylpyridines and the 2- and 4-methylquinolines were tautomeric in the sense,



and



That is to say, the group $CH_3\overset{|}{C}{=}N{-}$ is tautomeric with $CH_2{=}\overset{|}{C}{-}NH{-}$. In lepidine (4-methylquinoline, formula above) and in 4-methylpyridine the methyl is separated from the $=C=N-$ by the ($-CH=CH-$) group, and so behaves in the same manner as quinaldine (cf. 50a).

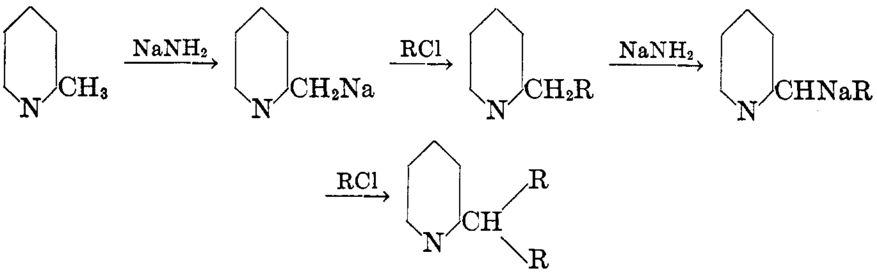
The tautomerism of quinaldine was discussed in an earlier article by one of us (3c) from the standpoint of the ammonia system, and it was seen that A and B (see formulas above) are related to one another as the keto modification is to its corresponding enol. (Chichibabin's article was referred to rather inadequately in reference 3c, although a statement to the contrary was made in reference 22.) Alkali amides convert quinaldine in liquid ammonia to very soluble, red, metallic salts, in which the metal, or rather the anionic charge, is located either on the side-chain carbon or on the nitrogen. (Ziegler and Zeiser (169) prefer the first formula.) 2-Alkylquinolines may readily be obtained by alkylating the potassium or sodium salts of quinaldine in liquid ammonia (3c) or the lithium salt in ether (169).

In 1914, Chichibabin and Seide (25) reported unsuccessful attempts to alkylate 2-methylpyridine by treating it simultaneously with sodium amide and methyl iodide, but, unfortunately, the Russian original was not available to us, and the abstracts did not mention it. In one experiment with ethyl iodide, sodium amide, and 2-methylpyridine, diethylamino-2-picoline was obtained, together with a small quantity of a base having the composition of a diethylaminopropylpyridine, but the work was not described until later (22).

Recently, Chichibabin has again taken up the question of alkylation of α- and γ-alkylquinolines and pyridines (22, 23). The reactions were usually carried out at room temperatures or slightly above with sodium amide, a 2- or 4-alkylpyridine or quinoline, or a 2,6-dialkylpyridine and an alkyl halide. The following directions are typical: The pyridine base is mixed in a round-bottom flask (reflux condenser) with an excess of finely pulverized sodium amide (which must be of very good quality). The liquid becomes colored yellow, then brown, or even brown-violet. The alkyl halide is added in small portions at a time, usually with cooling. With γ-picoline and quinaldine, it is necessary to cool during the entire reaction period. In some cases a little dry ether is added. The pyridine or quinoline base is usually in excess. The product is worked up after the mixture has stood overnight. The yield of alkylated products, if alkyl chlorides are used, is not inferior to 40 per cent, and is usually 50 to 60 per cent of the monosubstitution product, or 70 to 80 per cent, if disubstitution products are included.

The ease of formation of metallic derivatives varies strongly with different pyridine bases. γ-Picoline reacts much more readily than α-picoline; β-collidine (γ-methyl-β-ethylpyridine) differs little from α-picoline. 2,6-Dimethylpyridine is even less reactive than α-picoline.

The alkyl bromides and iodides, the latter in particular, are less satisfactory than the chlorides in this synthesis. The two principal reactions may be expressed by the representative equation below,



Among the compounds prepared are the following: 2-(ω-phenylethyl)-pyridine, 2-(dibenzylmethyl)pyridine, γ-phenylpropylpyridine, 2-*n*-amylpyridine, 2-isoamylpyridine, 2-cyclohexylmethylpyridine (hexahydrobenzylpyridine), 2-butenylpyridine (from sodium amide, allyl chloride, and 2-methylpyridine), 2-propylpyridine, 4-phenylethylpyridine, 4-isobutylpyridine, diisopropylpicoline, 4-*n*-amylpyridine, 4-(di-*n*-butylmethyl)-pyridine, 4-isoamylpyridine, 4-(diisobutylmethyl)pyridine, 4-propylquinoline (from lepidine, sodium amide, and ethyl iodide in 90 per cent yield), monobenzylquinaldine (65 per cent yield), and dibenzylquinaldine (25 per cent yield), the last two in the same reaction.

B. Quinoline, isoquinoline, and their derivatives[6]

In the previous review it was recorded that potassium amide and sodium amide react with quinoline in liquid ammonia at room temperatures to form resins, with occasional traces of 2-aminoquinoline (6, p. 158). It has now been found (7a) that the latter may be prepared in 50 to 55 per cent yield if the reaction is carried out in the presence of potassium nitrate, which is reduced to potassium nitrite in the process. The essential reaction is therefore the following:

$$C_9H_7N + 2KNH_2 + KNO_3 \rightarrow C_9H_6NNHK\text{-}2 + KOH + KNO_2 + NH_3$$

A 10 per cent yield of 4-aminoquinoline was also obtained in one experiment. An excess of a soluble amide (KNH_2) is necessary.

The reaction between barium amide and quinoline in liquid ammonia at room temperatures leads to the formation of both 2-aminoquinoline and hydrogen in good yields, in accordance with the equation (4),

$$2C_9H_7N + Ba(NH_2)_2 \rightarrow (C_9H_6NNH)_2Ba + H_2$$

$$(C_9H_6NNH)_2Ba + 2H_2O \rightarrow Ba(OH)_2 + 2C_9H_6NNH_2$$

The reaction occurs irrespective of the relative amounts of barium amide and quinoline. Barium ion appears to catalyze the reaction, which is greatly accelerated by ammonia-soluble barium salts such as the thiocyanate. Strontium amide is less effective than barium amide in the above, while no aminoquinoline can be obtained if the amides of lithium, sodium, or calcium are used. Potassium ammonobarate, $BaNK \cdot 2NH_3$, and quinoline also react to give aminoquinoline, presumably because of a slight dissociation of this salt into barium amide and potassium amide.

Isoquinoline reacts fairly rapidly with potassium amide in excess of one equivalent in liquid ammonia to form 1-aminoisoquinoline in yields as high as 83 per cent of the theoretical, together with hydrogen in somewhat larger quantity (5). If the isoquinoline is in excess of one molar proportion, the rate of formation of aminoisoquinoline is very slow. Therefore

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[6] See section XVII A for the mechanism of the action of sodium amide with heterocyclic nitrogen bases and for the alkylation of 2- and 4-alkylquinolines.

it appears that an excess of amido ions, NH_2^-, is necessary for a rapid reaction, and since potassium amide is the only readily available amide of high solubility in liquid ammonia, it follows that very little, or no 1-aminoisoquinoline should be formed from isoquinoline and the sparingly soluble amides of sodium, lithium, calcium, and magnesium, as indeed proved to be the case. Barium amide, in spite of a low solubility in ammonia, did give 1-aminoisoquinoline in 54 per cent yield, together with hydrogen, and the reaction was found to be markedly accelerated by the ammonia-soluble barium thiocyanate. It is significant that aminoisoquinoline and hydrogen are formed even when isoquinoline is in excess. It therefore appears that barium (or barium ion, more probably) exerts the same catalytic effect here as in the reaction between quinoline and barium amide. Strontium amide is inferior to barium amide in the conversion of isoquinoline into 1-aminoisoquinoline.

The importance of an excess of NH_2^- ions in the potassium amide–isoquinoline reaction was tentatively explained in the following manner:

(*1*) An addition compound is first formed (cf. section X B)

$$NH_2^- + \text{—}CH\text{=}N\text{—} = \text{—}CH(NH_2)\text{—}\bar{N}\text{—}$$

(The —CH=N— group of isoquinoline is alone represented, and the reaction is written ionically.)

(*2*) An excess of amide ions favors the reaction expressed by the following equation, read from left to right,

$$\text{—}CH(NH_2)\text{—}\bar{N}\text{—} + NH_2^- \rightleftharpoons \text{—}CH(\bar{N}H)\text{—}\bar{N}\text{—}$$

(*3*) The influence of the two anionic charges on the nitrogen cause the removal of hydrogen and an electron, which ammonia converts to H_2 and NH_2^-. In other words, potassium hydride is lost, as in the mechanism proposed by Ziegler and Zeiser for the sodium amide–pyridine reaction (168).

The ammono salts, $NaNK_2 \cdot 2NH_3$ and $BaNK \cdot 2NH_3$, reacted with isoquinoline to give 1-aminoisoquinoline and hydrogen, but $CaNK \cdot 2NH_3$, $SrNK \cdot 2NH_3$, and $Al(NH_2)_2NHK \cdot NH_3$ failed to do so.

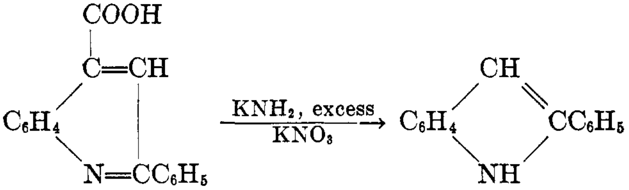
It has been shown experimentally (5, 7a) that isoquinoline and quinoline form addition compounds with the alkali amides in liquid ammonia. The potassium amide–quinoline addition compound, especially in the presence of an excess of NH_2^- ions, decomposes in time into resins, unless some reducible substance, such as potassium nitrate, is present (7a; see the first paragraph of this section).

2- or 4-Amino derivatives of homologues of quinoline are obtained by the action either of barium amide or of potassium nitrate and an excess of potassium amide in liquid ammonia on the substituted quinoline (7a).

Among other compounds, the following have been prepared: 4-amino-2-phenylquinoline in 92 to 100 per cent yield from 2-phenylquinoline; 4-aminoquinoline-2-carboxylic acid from quinoline-2-carboxylic acid (quinaldinic acid); 2-aminoquinoline-4-carboxylic acid from quinoline-4-carboxylic acid (cinchoninic acid); the 2(?)-amino derivatives of 6- and 8-phenylquinoline, 6-dimethylaminoquinoline, quinoline-6-sulfonic acid, quinoline-6-carboxylic acid, and 6-methoxyquinoline (a mixture is obtained if potassium amide and potassium nitrate are used). In most of these reactions the second procedure has been of more value, since with barium amide solubility relationships are often of importance. 2-Phenylquinoline, for example, does not react with barium amide, although it reacts very rapidly with potassium amide and potassium nitrate.

Competition experiments have shown that quinoline-2-carboxylic acid and 2-phenylquinoline react more readily than quinoline with potassium amide and potassium nitrate in liquid ammonia, while 2-hydroxy- and 2-amino-quinoline are not attacked at all under the same conditions. Therefore reactions of this type are accelerated by phenyl and carboxyl but hindered by hydroxyl and amino (the effect of the methyl group has not been determined), contrary to what has often been observed when substituted benzenes are nitrated or sulfonated. (The NH_2 group differs in polar character from NO_2 (77).)

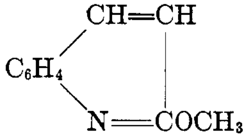
Cincophen (atophan, 2-phenylquinoline-4-carboxylic acid) undergoes a peculiar reaction with potassium amide and potassium nitrate in liquid ammonia at room temperatures, with the formation of 2-phenylindole (7a).



Since the latter is only formed when the water-soluble hydrolysate of the reaction product is boiled with water, it probably results by the ring closure of some intermediate. The reaction, the mechanism of which is at present unknown, is dependent in large measure upon the character of the substituents in the cinchophen. Thus, no indole derivative has been isolated by treating 2-*p*-tolyl-quinoline-4-carboxylic acid with potassium amide and potassium nitrate. 2-*p*-Methoxyphenyl indole, phenyl α-naphthindole (= 2-phenyl-6,7-benzindole), and some others have been prepared by this reaction.

Quinoline-2-sulfonic acid is readily converted by a liquid ammonia solution of potassium amide at room temperatures into 2-aminoquinoline (74 per cent yield), showing that a sulfonic acid group, as well as a halogen in position 2, has an enhanced reactivity (7a). A patent has recently been granted, in which it is stated that 2-aminoquinoline may be formed by heating quinoline-2-sulfonic acid with aqueous ammonia and zinc chloride (78a).

2-Methoxyquinoline,



is formally a cyclic neutral aquoammono ester, by virtue of the grouping $—C(=NR)OCH_3$. It is therefore not surprising to find that a solution of potassium amide in liquid ammonia readily saponifies it to 2-aminoquinoline, the corresponding cyclic acid-ester of the ammonia system (64 per cent yield) (7a).

2-Methylquinoline, 2-methyl-5,6-benzoquinoline, and 2,3-dimethylquinoxaline react with potassium amide in liquid ammonia to give potassium salts, from which orange or yellow ketones may be obtained in a Claisen-type condensation, in accordance with the type equation,

$$C_9H_6NCH_3 \xrightarrow[NH_3]{KNH_2} \underset{A}{C_9H_6NCH_2K \text{ (or } C_9H_6NK{=}CH_2)} \xrightarrow[\text{in ether}]{C_6H_5COOC_2H_5}$$

$$\underset{\substack{\text{2-Phenacylquinoline} \\ \text{(60 to 65 per cent yield)}}}{C_9H_6NCH_2COC_6H_5} + C_2H_5OK$$

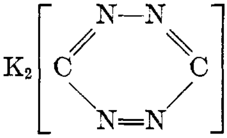
For the purpose of convenience, the first step in the reaction is carried out in liquid ammonia, which is later evaporated and replaced by ether, although this latter solvent doubtless could have been used from the start. Two to three moles of potassium amide should be used for each mole of quinaldine, for otherwise the phenacylquinoline forms a potassium salt at the expense of the potassium quinaldyl (A), regenerating quinaldine.

2-*p*-Methylphenacylquinoline, 2-*p*-methoxyphenacylquinoline, 2-*o*-chlorophenacylquinoline, 2-*p*-bromophenacylquinoline, 2-phenacyl-5,6-benzoquinoline, 2-*p*-methoxyphenacyl-5,6-benzoquinoline, 2-furoylquinaldine, and monobenzoyl-2,3-dimethylquinoxaline have been synthesized. Esters of aliphatic acids and many 2- or 4-alkylated quinolines whose potassium salts are insoluble in ether fail to react to give definite products (109).

Renfrew and Cretcher (123) were unable to introduce an amino group into cinchonine or hydroquinine by means of sodium amide in boiling xylene. Instead there were obtained fairly good yields of the corresponding ketones, cinchininone (21 per cent) and hydroquininone (40 per cent).

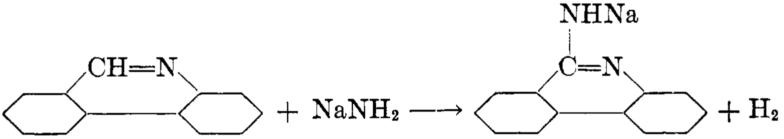
E. Tetrazine

Tetrazine and potassium amide in liquid ammonia react to form a red dipotassium salt of the probable constitution (157; cf. 6, p. 163),



F. Phenanthridine

Morgan and Walls (110) made 9-aminophenanthridine by heating phenanthridine with sodium amide under xylene at 110–130°C., in accordance with the equation,

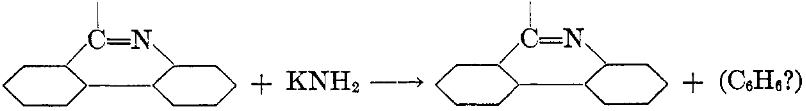


Sodium salt of 9-amino-phenanthridine

The average yield was about 60 per cent; the maximum yield 80 per cent.

Gee (50b) and Bergstrom (7a) have found that phenanthridine reacts with an excess of potassium amide in liquid ammonia to give hydrogen in almost quantitative yield and aminophenanthridine in quantities upward of 90 per cent of the theoretical. 9-Methylphenanthridine, like quinaldine, reacts with potassium amide to form a potassium salt.

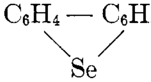
9-Phenylphenanthridine, since it contains the grouping $C_6H_5\text{—}\overset{\overset{\displaystyle R}{|}}{C}\text{=N—}$, is a cyclic ketone-ether of the ammonia system, and, as such, reacts with potassium amide, with potassium amide and potassium nitrate, or with barium amide to form 9-aminophenanthridine, in the sense of the equation,



The benzene has not been identified.

It will be recalled that benzophenone undergoes scission to benzamide and benzene when heated with sodium amide (6, p. 122).

XIX. MISCELLANEOUS

Diphenyl selenoxide, $(C_6H_5)_2SeO$, and sodium amide react to give diphenylene selenide,  $\underset{Se}{C_6H_4 - C_6H_4}$, and $C_6H_5SeO_2$ (33; cf. 6, pp. 164–5, concerning the action of $NaNH_2$ on $(C_6H_5)_2SO$).

Kraus and Hawes (91) have prepared $NaNH_2 \cdot B(C_6H_5)_3 \cdot 3NH_3$ and $KNH_2 \cdot B(C_6H_5)_3 \cdot NH_3$ for conductivity measurements by treating boron triphenyl with sodium amide or potassium amide in liquid ammonia.

The preparation and use of alkyl substitution products of the alkali amides, such as $(C_2H_5)_2NLi$ and cyclohexyl$\cdot$NHNa, has been described in sections I, VI A and D, and XII C and F (161, 162, 163, 166, 167, 74, 3a).

Staudinger and Lohmann (139) find that sodium amide slowly polymerizes ethylene oxide to a product having a molecular weight of around 10,000 (two to three months reaction).

Kraus and Toonder (95) find that the reaction between sodium amide and trimethyl gallium in liquid ammonia follows the equation,

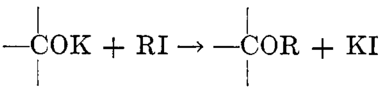
$$NaNH_2 + 2(CH_3)_3Ga \rightarrow [(CH_3)_3Ga]_2 \cdot NaNH_2$$

Although the methane hydrogen of triphenylmethane may readily be replaced by alkali metals, Kraus and Nelson (94) found that triethylsilicane undergoes the following peculiar reaction in liquid ammonia,

$$2(C_2H_5)_3SiH + KNH_2 \rightarrow [(C_2H_5)_3Si]_2NK + 2H_2$$

This recalls the reaction between the alkali amides and heterocyclic nitrogen bases of the type of pyridine, quinoline, and isoquinoline, in which amino derivatives are formed with the evolution of hydrogen (6, pp. 154–161; also section XVII A and B).

Muskat (112) prepared polypotassium salts of sugars in which the reducing group was suitably blocked by the action on them of potassium amide (or metallic potassium or sodium) in liquid ammonia at −33°C. These salts react with methyl iodide, either in the presence or absence of solvent, to form methylated sugars, in sufficiently good yields to make this method valuable. The principal reaction is expressed by the equation,



$$-\underset{|}{\overset{|}{C}}OK + RI \rightarrow -\underset{|}{\overset{|}{C}}OR + KI$$

but the following side reactions may occur:

$$NH_3 + RI \rightarrow R_4NI + NH_4I \quad \text{(equations are not balanced)}$$

$$-\overset{|}{\underset{|}{C}}OK + R_3NHI \rightarrow -\overset{|}{\underset{|}{C}}OH + NR_3 + KI$$

$$-\overset{|}{\underset{|}{C}}OK + NH_4I \rightarrow -\overset{|}{\underset{|}{C}}OH + NH_3 + KI$$

As a general procedure, where the reactivities of the alkali metal salts of the carbohydrates and of the substituting reagent are unknown, it is advisable to remove the ammonia after the formation of the salt, and add the reagent in an inert medium. The following reactions are among those that have been carried out:

$$\text{K salt of diacetoneglucose} + CH_3I \xrightarrow{\text{ether}} \text{3-methyldiacetoneglucose}$$

$$\text{K salt of diacetoneglucose} + CH_3COCl \xrightarrow{\text{ether}} \text{3-acetyldiacetoneglucose}$$

$$\alpha\text{-Methylmannoside} \xrightarrow[\text{poly-K salt}]{\text{alkylation of}} \text{tetramethyl-}\alpha\text{-methylmannoside}$$

Miller and Siehrs (108) prepared monopotassium salts of the monosaccharides and dipotassium salts of the disaccharides by the action of potassium amide on concentrated liquid ammonia solutions of the sugars at −33°C. As a rule these are stable in the air when dry, that is, when freed from solvent ammonia. Glycogen, however, gives a salt which chars on exposure to air. Reducing sugars are caramelized by potassium amide in liquid ammonia at room temperatures within a day, while sucrose is stable.

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Errors in part II of the previous review (6)

p. 84. Middle of the page: change "potassium cyanide" to "sodium cyanide."

p. 85. Bottom: change second line from bottom to read "cyanamide (as an alkali metal salt) is the only ammonocarbonic acid formed." Delete "disodium."

p. 106. First line: after "phenyl group" add "attached to nitrogen."

p. 109. Twelfth line: substitute "usually" for "often."

p. 119. Third line above formulas: add (167) after "position."

First line above formulas: substitute "(216, cf. 167)" for "(216)."

Bottom two lines: change to read ". . . . also causes a second radical to enter the α'-position (166, 216b, as corrected by Cornubert and Humeau (Bull. soc. chim. [4] **49**, 1494–7 (1931))."

p. 123. Eleventh line from bottom: substitute "hydrocarbon" for "hydrecarbon."

p. 164. Section XVIII A, sixth line: $S(=NH)_2$ is correct.

p. 169. Reference 75: change "Ber. **26**" to "Ber. **36**."

p. 170. Reference 170 should have "(1931)" in place of "(1921)."

p. 173. Reference 216: designate the first reference (a) and the second (b).

p. 175. Reference 270: change "(1913)" to "(1912)."

AUTHOR INDEX

Volumes 11 to 20