THE APPLICATION OF THE GRIGNARD REACTION TO ALKALOID SYNTHESES

and two additional papers,

THE REDUCTION OF α-AMINO-NITRILES

and

THE INTERACTION OF α-AMINO-NITRILES AND THE GRIGNARD REAGENT.

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THE APPLICATION OF THE GRIGNARD REACTION

TO ALKALOID SYNTHESES.

INTRODUCTION.

An α-amino-nitrile and a Grignard reagent may react in one of three ways; they may undergo 'normal' ketone formation (I), or double decomposition, the nitrile group being replaced by the radical of the Grignard reagent (II), or a Fittig-Wurtz reaction (III).

$$R_1 R_2 \cdot C \cdot CN + R_5 MgX \;\;\substack{N \cdot R_3 R_4}$$

$$R_1 R_2 C \cdot CO \cdot R_5 \qquad \text{I.}$$
$$N \cdot R_3 R_4$$

$$R_1 R_2 C \cdot R_5 \qquad \text{II.}$$
$$N \cdot R_3 R_4$$

$$\left[R_1 R_2 \cdot C \cdot \atop N \cdot R_3 R_4 \right]_2 \qquad \text{III.}$$
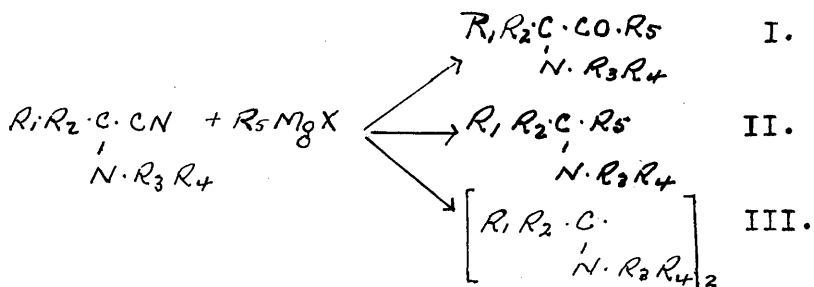
It has been found that double decomposition occurs with a large number of tertiary α-amino-nitriles. The conditions favouring (II) have been fairly well established, and the yields are such as to make the reaction a method of considerable synthetical importance for the preparation of tertiary amines.[1,2,ϕ]

Accordingly, it was thought that the reaction might be employed for the preparation of some alkaloids, many of which contain an α-substituent in the heterocyclic ring. The nitriles chosen for the investigation were 1-cyano-2-methyl-6:7-dimethoxy-1:2:3:4-tetrahydroisoquinoline (IV) and α-cyano-N-methylpyrrolidine (V).
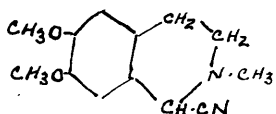
IV.
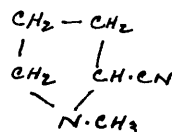
V.

ϕ This reaction is discussed more fully on p. 54.

By interaction with suitable Grignard reagents it was hoped
to prepare Laudanosine (VI) and Carnegine (VII) from IV, and
Nicotine (VIII) and Hygrine (IX) from V, the latter possibly
by treating the nitrile with β-methoxy-n-propyl-magnesium
chloride, followed by replacement of the methoxyl group by
hydroxyl and oxidation.
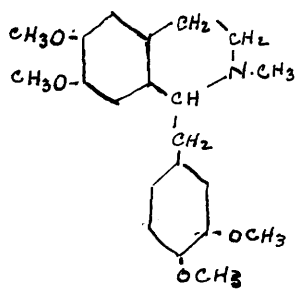
(VI.)   (VII.)
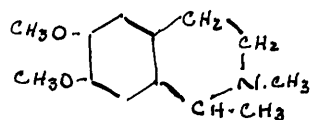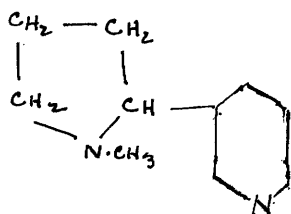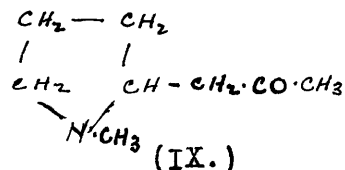
(VIIL)   (IX.)

Both series of experiments were unsuccessful; various
methods for the preparation of α-Cyano-N-methyl pyrrolidine
were tried and in all cases negative results were obtained.
After considerable difficulty 1-Cyano-2-methyl-6: 7-dimethoxy-
1:2:3:4 tetrahydroisoquinoline was obtained, but it was
found that this nitrile does not react on treatment with
Grignard Reagents.

DISCUSSION.

PART I.

1-Cyano-2-methyl-6: 7-dimethoxy-1: 2: 3: 4-tetra-hydroisoquinoline. (IV)

It was anticipated that Carnegine (VII), whose con-
stitution has only recently been established[3] and which was
therefore of considerable interest, would be produced by the
action of methyl magnesium iodide upon the above nitrile:-
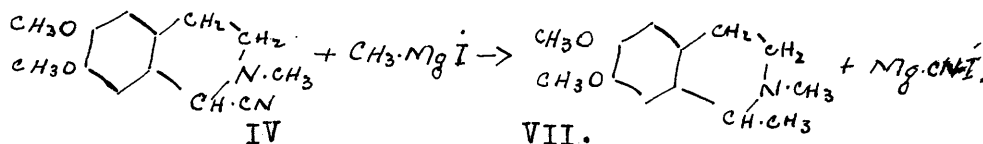
Unfortunately the expected product was not obtained. In a
series of experiments carried out under varying conditions
unchanged nitrile was the only substance which could be is-
olated. This result was surprising in view of the fact that
the corresponding methylenedioxy compound, 1-cyanohydro-
hydrastinine, reacts with methyl magnesium iodide to produce
1-methyl-hydrohydrastinine.[1]

The non-reactivity of the nitrile towards Grignard
reagents made the synthesis of Laudanosine (VI) impossible,
but since the preparation of the nitrile was a very slow pro-
cess, experiments for the discovery of a suitable Grignard re-
agent for the preparation of that alkaloid were undertaken
before the above facts were known. The most suitable halides

were 3: 4-dimethoxy-benzyl chloride and the corresponding bromide. According to Decker and Pschorr, however, these substances do not form magnesium compounds,[4] but since Robinson and Robinson state that the magnesium derivative of 3: 4-methylenedioxy-benzyl bromide is easily produced,[5] a re-investigation of this matter was considered advisable. The results of the German workers were confirmed.

In order to overcome this difficulty 3-methoxy-4-benzyloxy-benzyl chloride was prepared and examined for the formation of a magnesium derivative. While it did not form a Grignard reagent easily, it was found to react with activated magnesium.

It was supposed that the nitrile and 3-methoxy-4-benzyloxy-benzyl-magnesium chloride (X) would produce 1-(3'-methoxy-4'-benzyloxy) -benzyl-2-methyl-6: 7-dimethoxy-tetrahydroisoquinoline (Xa), which, after removal of the 4'-benzyl group by treatment with hydrochloric acid[ϕ] and subsequent methylation, would yield Laudanosine.

ϕ This method has been employed frequently for the removal of the benzyl group in benzyloxy compounds. For example, 3-methoxy-4-benzyloxy-benzaldehyde passes to vanillin on standing with strong hydrochloric acid.

(Boehringer and Söhne, D.R.P., 65937; Frdl. 3, 897.)

(X).

(Xa)

$\xrightarrow{HCl}$

$\xrightarrow{Methylation}$
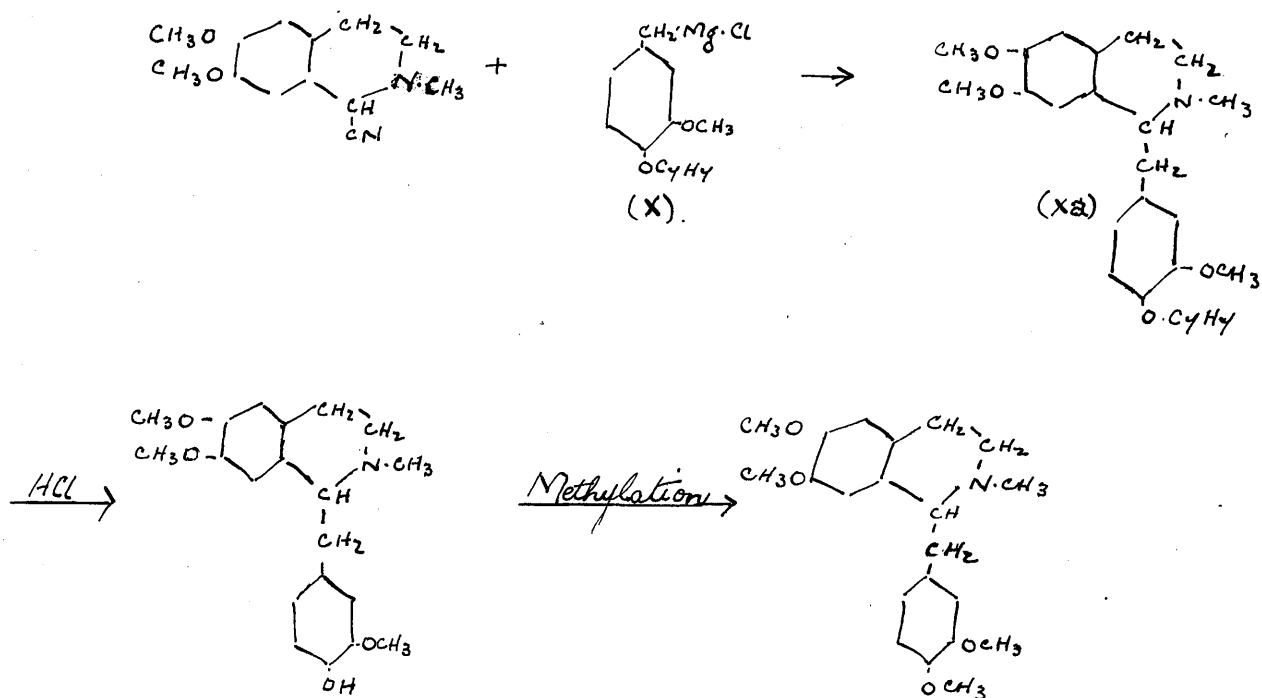
Owing to the stability of the nitrile, these proposed steps could not be tested experimentally.

Synthesis of l-cyano-2-methyl-6: 7-dimethoxy-tetrahydroisoquinoline.

This substance was first described by Pyman who prepared it as a derivative of 4:5-dimethoxy-2-β-methyl-amino-ethyl-benzaldehyde (XI); he obtained the aldehyde, along with a considerable quantity of veratraldehyde, by the oxidation of Laudanosine with pyrolusite.[6] More recently the nitrile has been synthesised by Buck,[7] in ignorance of whose work most of the following experiments were performed.

or

(XI)
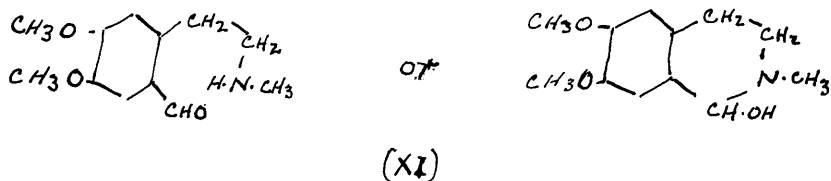
The synthesis was carried out in the following stages. Veratraldehyde (XIII) was prepared by methylating vanillin (XII),[8] and condensed with malonic acid; the resultant 3:4-dimethoxy-cinnamic acid (XIV) was reduced with sodium amalgam to β-3: 4-dimethoxy-phenylpropionic acid (XV),[9] and then the product was converted to the amide (XVI).[10,11] By the application of
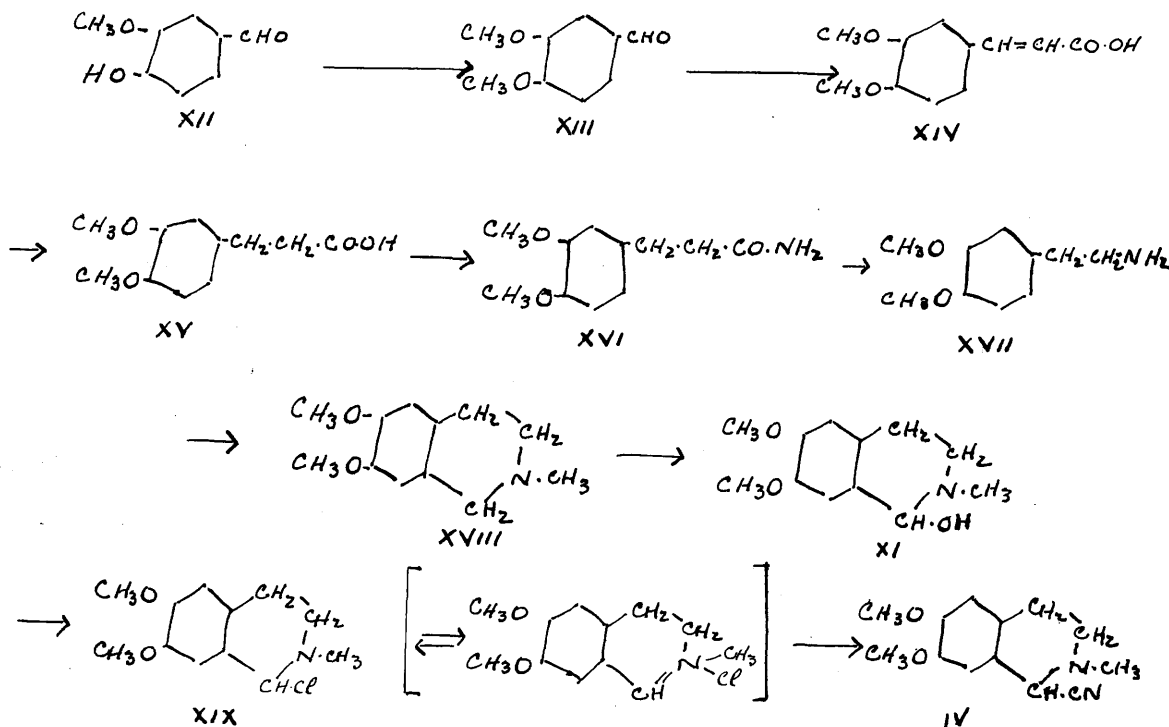
Hofmann's reaction the amide was converted to β-veratryl-ethylamine (XVII),[12] which, on heating with formaldehyde under pressure, gave 2-methyl-6:7-dimethoxy-1:2:3:4-tetrahydro-isoquinoline (XVIII). The latter was oxidised to 4:5-dimeth-oxy-2-β-methylaminoethyl-benzaldehyde (XI)[13] from which the

chloride (XIX) was prepared. The nitrile (IV) was obtained by the addition of potassium cyanide to an aqueous solution of the chloride.[6.]

At first unsatisfactory yields were obtained in the conversion of β-3: 4-dimethoxy-phenyl propionic acid to its amide, and, in an attempt to find an alternative method for the preparation of β-veratrylethylamine, unsuccessful efforts were made to reduce 3: 4-dimethoxy-ω-nitrostyrene (XX) with sodium and alcohol.

$$CH_3O \quad \text{(ring)} \quad -CH=CH \cdot NO_2 \qquad XX$$
$$CH_3O$$
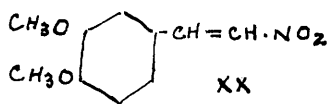
In addition to the procedure outlined above 4: 5-dimethoxy-2-β-methylaminoethyl-benzaldehyde was prepared from β-veratrylethylamine by the method employed by Buck.[7] The amine was first methylated via the Schiff's base (XXI), and then converted to N-formyl-N-methyl-β-veratrylethylamine (XXII). The aldehyde (XI) was obtained by heating the latter with phosphorus pentoxide and then pouring the reaction mixture into water and making the aqueous solution alkaline.

$$CH_3O \quad \text{(ring)} \quad -CH_2 \cdot CH_2 \cdot NH_2 \quad \rightarrow \quad -CH_2 \cdot CH_2 \cdot N = CH \cdot C_6H_5 \quad \rightarrow \quad -CH_2 \cdot CH_2 \cdot N\!\!<^H_{CH_3}$$
$$CH_3O \qquad\qquad\qquad\qquad XXI$$

$$\rightarrow \quad \begin{array}{c} CH_2\text{-}CH_2 \\ | \\ N \cdot CH_3 \\ | \\ CHO \end{array} \quad XXII \quad \rightarrow \quad \left[\begin{array}{c} CH_2\text{-}CH_2 \\ CH_3 \cdot N \cdot PO_4H_2 \\ \| \\ CH \end{array} \right] \quad \rightarrow \quad \begin{array}{c} CH_2\text{-}CH_2 \\ | \\ N \cdot CH_3 \\ | \\ CH \cdot OH \end{array} \quad XI$$
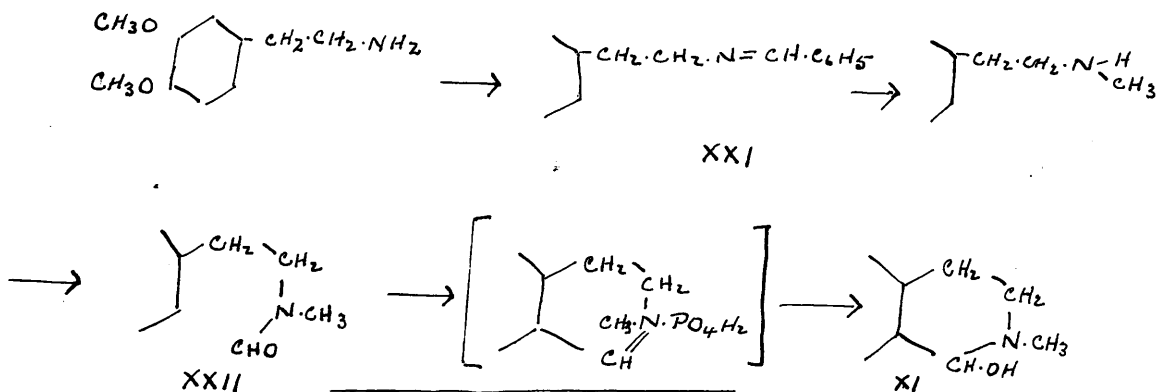
PART II.

α-Cyano-N-methylpyrrolidine (V).

The preparation of this nitrile was undertaken for the purpose of preparing from it some alkaloids containing an α-substituted N-methylpyrrolidine ring. For example it was hoped to prepare nicotine (VIII) by the action of β-pyridyl magnesium bromide upon the nitrile.
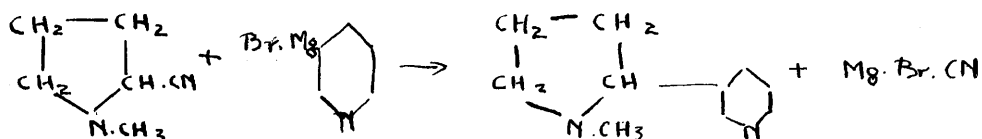
Before these experiments were started no general method for the preparation of α-substituted N-methylpyrrolidines had been published, but during the investigation the preparation of a number of such substances was described by Craig. Craig[14] and, independently, Lukes[15] had evolved the same method for the preparation of α-substituted N-methylpyrrolines and the former extended it to N-methylpyrrolidines.[16] N-methylpyrrolidone, prepared by the electrolytic reduction of N-methyl-succinimide, was treated with a Grignard reagent, and on hydrolysis of the addition compound with hydrochloric acid an α-substituted N-methylpyrroline was obtained. In some cases the latter was reduced by addition of magnesium to the strongly acid reaction mixture, but in others it was necessary to isolate the pyrroline and reduce it by other means. For example, α-methyl-N-methylpyrroline was isolated and then reduced electrolytically. The stages, starting from N-methyl-succinimide, are indicated

in the following scheme.

$$CH_2 - CH_2, \quad CO \quad CO, \quad N \cdot CH_3 \quad \longrightarrow \quad CH_2 - CH_2, \quad CH_2 \quad CO, \quad N \cdot CH_3 \quad \longrightarrow \quad CH_2 - CH_2, \quad CH_2 \quad C \overset{OMgX}{\underset{R}{\diagdown}}, \quad N \cdot CH_3$$

$$\xrightarrow{\text{hydrolysis and heat.}} \quad CH_2 - CH, \quad CH_2 \quad C \cdot R, \quad N \cdot CH_3 \quad \longrightarrow \quad CH_2 - CH_2, \quad CH_2 \quad CH \cdot R, \quad N \cdot CH_3$$

It was thought that the above type of compound, which is of considerable interest in studies on the relationship between chemical constitution and physiological action,[14] might be obtained more easily from α-cyano-N-methylpyrrolidine. Unfortunately all the schemes devised for the preparation of the nitrile were unsuccessful.

The possibility of starting from proline (XXIV) was considered first of all. The steps necessary for its conversion to the nitrile are -

$$CH_2 - CH_2, \quad CH_2 \quad CH \cdot COOH, \quad N \cdot H \quad \xrightarrow{\text{Methylation}} \quad CH_2 - CH_2, \quad CH_2 \quad CH \cdot COOH, \quad N \cdot CH_3 \quad \longrightarrow \quad CH_2 - CH_2, \quad CH_2 \quad CH \cdot CONH_2, \quad N \cdot CH_3 \quad \longrightarrow \quad CH_2 - CH_2, \quad CH_2 \quad CH \cdot CN, \quad N \cdot CH_3$$

XXIV.   XXV.

Proline, however, is extremely difficult to obtain in quantity either by synthetical methods or by separation from the other amino-acids in hydrolysed protein,[17] and while methylation might be effected without undue difficulty it is extremely doubtful if the resultant hygric acid (XXV) would

be sufficiently stable to withstand the treatment necessary for its conversion to the nitrile. The idea was therefore abandoned.

(A) A process analogous to Willstätter and Ettlinger's synthesis of hygric acid[18] was tried out. The proposed stages were as follows. Trimethylene bromide was to be condensed with the sodium derivative of cyano-acetic ester giving γ-bromopropyl-cyanoacetic ester (XXVI) and then the ester was to be converted to the acid. It was anticipated that the bromination of the acid would be accompanied by elimination of carbon dioxide and would result in the production of 1: 4-dibromo-1-cyanobutane[ɸ] (XXVII) which, on treatment with mono-methylamine, would yield the nitrile (V)

$$Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot Br + Na \cdot CH \underset{CO \cdot OC_2H_5}{\overset{CN}{<}} \longrightarrow Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH \underset{COOC_2H_5}{\overset{CN}{<}}$$
XXVI

$$\longrightarrow Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH \underset{CO \cdot OH}{\overset{CN}{<}} \longrightarrow Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH \underset{Br}{\overset{CN}{<}}$$
XXVII

$$\xrightarrow{H_2N \cdot CH_3} \quad \begin{matrix} CH_2 - CH_2 \\ | \qquad | \\ CH_2 \quad CH \cdot CN \\ \diagdown \quad \diagup \\ V \quad N \cdot CH_3 \end{matrix}$$
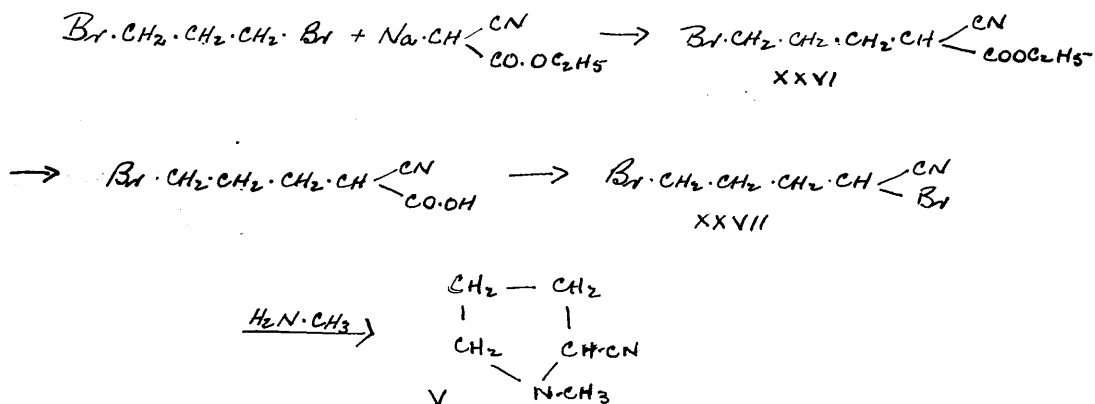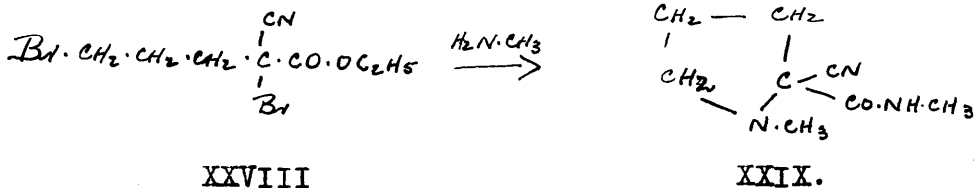
The condensation of trimethylene bromide and sodio-cyanoacetic ester gave only a small yield of γ-bromopropyl-
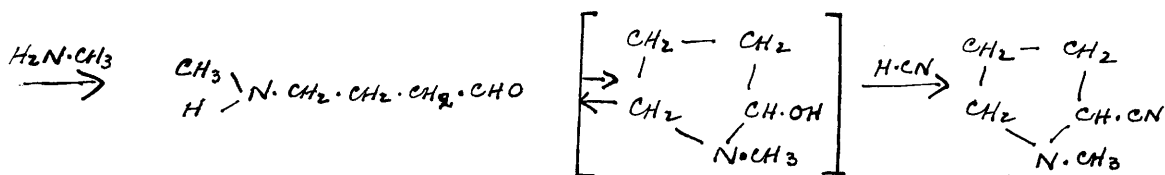

[ɸ] This was based upon the observation by Baker and Lapworth that the bromination of benzylcyanoacetic acid is accompanied by evolution of carbon dioxide and results in the formation of α-bromo-β-phenylpropionitrile. The yield is over 90%.[19]

cyanoacetic ester, and all efforts to hydrolyse the latter were unsuccessful. The hydrolysis was complicated by the presence of the bromine atom and the nitrile group in the molecule. Alkaline reagents could not be used since they would have converted the bromo-acid to a lactone, while acid conditions were liable to bring about conversion of the cyano-group to -COOH. Accordingly only mildly acid conditions were employed but the experiments were unsuccessful, and the process could not be continued.

In Willstätter and Ettlinger's synthesis of hygric acid no attempt was made to hydrolyse the γ-bromopropyl-malonic ester prepared by the condensation of trimethylene bromide and sodio-malonic ester; the ester itself was brominated.[18] A similar procedure in the present investigation would have produced $\alpha:\delta$-dibromo-α-cyano-n-valeric ester (XXVIII) and the latter on treatment with monomethylamine would probably have given the methylamide of 1-methyl-2-cyano-pyrrolidine-2-carboxylic acid (XXIX).

$$Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot \underset{\underset{Br}{|}}{\overset{\overset{CN}{|}}{C}} \cdot CO \cdot OC_2H_5 \xrightarrow{H_2N \cdot CH_3}$$

XXVIII   XXIX.
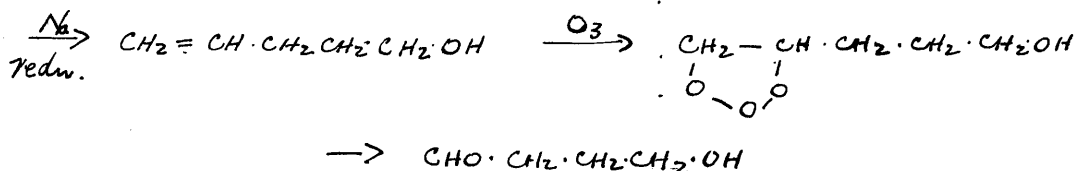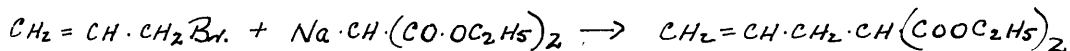
The prospect of successfully removing the $- CO \cdot NH \cdot CH_3$ group without otherwise altering the compound XXIX was considered to be very slight and no attempt was made to test the process experimentally.
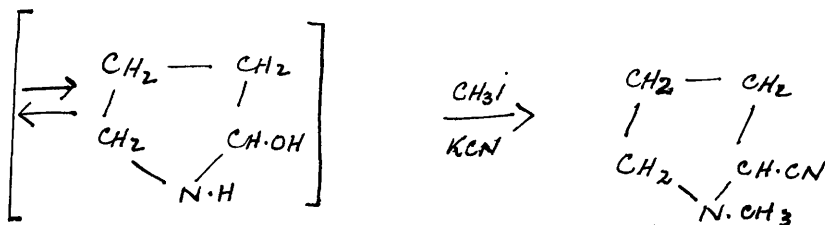
The possibility of employing the methylamide in Grignard reactions for the preparation of α-substituted N-methylpyrrolidines was also considered, but as before the scheme was thought to be too complicated for successful experimentation. In addition to the assumption of preferential action of the Grignard reagent at the cyano-group as compared with the methylamido-group, it would have involved the subsequent elimination of the carboxylic group in the product of the Grignard reaction. The possible stages are shown below.

(B.) In 1925 Stephen published a method for the preparation of aldehydes from nitriles.[20] The nitrile was treated with stannous chloride dissolved in anhydrous ethereal hydrogen chloride and the aldimine stannichloride which separated from the reaction mixture was converted to the aldehyde by heating with water. It was thought that this reaction might provide a suitable method for the conversion of γ-chlorobutyronitrile to γ-chlorobutyraldehyde, an intermediate step in the preparation of α-cyano-N-methylpyrrolidine by the following route.

$$H_2N{\cdot}CH_3 \longrightarrow \quad {}^{CH_3}_{H}\!\!\searrow\!\! N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHO \quad \left[\begin{array}{c} CH_2 - CH_2 \\ | \qquad | \\ CH_2 \quad CH{\cdot}OH \\ \searrow N{\cdot}CH_3 \end{array} \right] \xrightarrow{H{\cdot}CN} \begin{array}{c} CH_2 - CH_2 \\ | \qquad | \\ CH_2 \quad CH{\cdot}CN \\ \searrow N{\cdot}CH_3 \end{array}$$
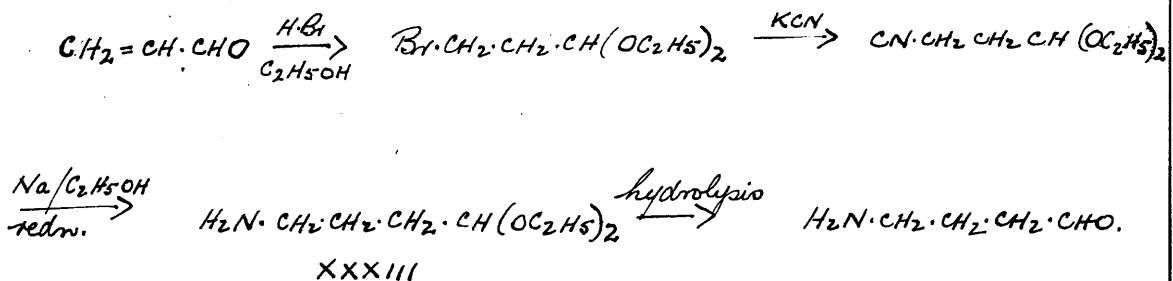
As indicated above it was intended to convert γ-chloro-butyraldehyde to γ-methylamino-butyraldehyde and it was expected that the latter would yield α-cyano-N-methyl-pyrrolidine on treatment with hydrocyanic acid.

γ-chlorobutyronitrile (XXX) was prepared from allyl alcohol by the stages shown above, but it could not be converted to the aldehyde (XXXII) by Stephen's method. The nitrile was treated with stannous chloride over a prolonged period, but no separation of the aldimine stannichloride (XXXII) was observed, and on working up the reaction mixture only unchanged nitrile was obtained. Stephen's method would appear not to be of much value with lower aliphatic nitriles; King and Robinson have reported great difficulty in preparing γ-methoxy-α-methyl-butyraldehyde from the corresponding nitrile by the same method.[21]

γ-hydroxy-butyraldehyde is a known substance, but the preparation of γ-chlorobutyraldehyde from it was rejected in view of the poor yields obtained by Helferich and Schäfer in practically every stage in their synthesis of the compound; these low yields would have made the preparation of a suffic-ient quantity of material extremely slow and laborious. Hel-ferich and Schäfer prepared γ-hydroxy-butyr-aldehyde in the following manner.[22]

$$CH_2 = CH \cdot CH_2 Br. + Na \cdot CH \cdot (CO \cdot OC_2H_5)_2 \longrightarrow CH_2 = CH \cdot CH_2 \cdot CH (COOC_2H_5)_2$$

$$\xrightarrow[\text{redu.}]{Na} CH_2 = CH \cdot CH_2 CH_2 \cdot CH_2 \cdot OH \xrightarrow{O_3} CH_2 - CH \cdot CH_2 \cdot CH_2 \cdot CH_2 OH$$

(with O, O, O bridge)

$$\longrightarrow CHO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$$

(C.) A third process for the preparation of α-cyano-N-methylpyrrolidine was tried out. The proposed stages are indicated in the scheme:

$$CH_2 = CH \cdot CHO \xrightarrow[C_2H_5OH]{H \cdot Br} Br \cdot CH_2 \cdot CH_2 \cdot CH (OC_2H_5)_2 \xrightarrow{KCN} CN \cdot CH_2 \cdot CH_2 \cdot CH (OC_2H_5)_2$$

$$\xrightarrow[\text{redu.}]{Na/C_2H_5OH} H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH (OC_2H_5)_2 \xrightarrow{hydrolysis} H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHO.$$

XXXIII

γ-Amino-butyraldehyde diethylacetal (XXXIII) was prepared from Acrolein by the reactions indicated above, but negative results were obtained in all efforts to convert it to the free aldehyde. Wohl, Schäfer, and Thiele prepared the acetal and made unsuccessful attempts to prepare the aldehyde; they were also unsuccessful in their efforts to prepare the pure oxalate of γ-amino-butyraldehyde.[23]

EXPERIMENTAL.

PART I.

<u>Veratraldehyde</u>. This compound was employed frequently in the following experiments and was prepared by methylating vanillin in methyl alcoholic solution with dimethyl sulphate (Perkin and Robinson, J.C.S., 1907, <u>91</u>, 1079).

<u>3:4-Dimethoxy-benzyl chloride</u>. By the application of Cannizzaro's reaction 3: 4-dimethoxy-benzyl alcohol was obtained from veratraldehyde (Decker and Pschorr, Ber., 1904, <u>37</u>, 3403), and was converted to the chloride by the action of hydrogen chloride in anhydrous ether. (Tiffeneau, Bull. Soc. Chim., 1911, (4), <u>9</u>, 930.)

On adding magnesium turnings to a solution of the chloride in anhydrous ether no reaction was observed. The application of heat and the addition of a crystal of iodine had no effect. Negative results were also obtained with magnesium-copper couple. Similar observations were recorded by Decker and Pschorr (ibid.).

<u>3-Methoxy-4-benzyloxy-benzyl chloride</u>. 3-Methoxy-4-benzyloxy-benzaldehyde was prepared from vanillin and subjected to Cannizzaro's reaction when a mixture of 3-methoxy-4-benzyloxy-benzyl alcohol and 3-methoxy-4-benzyloxy-benzoic acid was produced. The alcohol was converted to the chloride by the action of hydrogen chloride in ethereal solution.

3-methoxy-4-benzyloxy-benzaldehyde was conveniently

prepared from vanillin in the following manner. 80 grams potassium carbonate were added to a solution of 50 grams vanillin and 50 grams benzyl chloride in 250 c.c.s. ethyl alcohol. The mixture was heated under reflux for 10 hours after which the alcohol was evaporated off. Unchanged benzyl chloride was then removed by steam distillation, and the residue, after being shaken with dilute caustic soda, was separated from moisture by dissolving in hot carbon tetrachloride. On evaporation of the solvent the product was obtained as a pale yellow oil which solidified on cooling. The yield of 68 grams was equivalent to 86% of the theoretical. The substance so obtained melted at 62°C. (the pure compound melts at 63-64°C. - D.R.P. 65937.), and was used in the next stage without further purification.

24 grams 3-methoxy-4-benzyloxy-benzaldehyde were mixed with 13 grams potassium hydroxide dissolved in 17 c.c.s. water, and sufficient methyl alcohol was added to produce a homogeneous solution on boiling. After heating under reflux for 15 hours the alcohol was distilled off and water was added. This addition caused the separation of a considerable quantity of oil which was removed by extraction with ether. The ethereal solution and the remaining aqueous solution were treated separately.

After washing with water, unchanged aldehyde was removed from the ethereal solution by shaking with a saturated solution of sodium bisulphite; the ether was washed again and dried over potassium carbonate. The solvent was distilled

off leaving a slightly yellowish oil which solidified on
cooling. After recrystallisation from benzene the product,
3-methoxy-4-benzyloxy-benzyl alcohol, was obtained as colour-
less, well developed needles melting at 72°C. The yield was
9 grams.

Analysis:

   Found   C = 73.5%: H = 6.7%

$C_{15}H_{16}O_{3}$ requires C = 73.8%; H = 6.6%

The aqueous layer was acidified with strong hydrochlor-
ic acid and the precipitate was filtered off and dried in a
vacuum desiccator. This 3-methoxy-4-benzyloxy-benzoic acid
was recrystallised from benzene; it was deposited in the form
of small colourless needles, m.pt. 170°C. The yield was 10
grams.

Analysis:

   Found   C = 69.5%; H = 5.6%

$C_{15}H_{14}O_{4}$ requires C = 69.8%; H = 5.4%

3-methoxy-4-benzyloxy-benzyl chloride was prepared by
dissolving the alcohol in dry ethereal hydrogen chloride. The
solvent was removed in a vacuum desiccator containing separate
quantities of potassium hydroxide and sulphuric acid. The
product was obtained as a white crystalline solid which was
deposited from low-boiling petroleum ether as colourless prisms,

m.pt. 73°C.; the mixed m.pt. of the chloride and the alcohol was 60°C.

Analysis:

$$\text{Found chlorine} = 13.3\%$$
$$C_{15}H_{15}O_2Cl \text{ requires chlorine} = 13.5\%$$

To a solution of the chloride in ether excess magnesium turnings were added; no reaction occurred. A piece of magnesium, previously activated by immersion in an ethereal solution of methyl iodide, continued to react when added to the chloride dissolved in ether. Some magnesium-copper couple was added to an anhydrous ethereal solution of the chloride; a faint reaction which became more pronounced on heating, took place. This reaction was not investigated further.

Synthesis of 1-Cyano-2-methyl-6: 7-dimethoxy-1:2:3:4-tetra-hydroisoquinoline.

The majority of the steps employed in this synthesis have been described in the literature, but this is the first occasion, with the exception of Buck's recent synthesis of Iodal,[ø] on which they have been employed in a preparation of this type.

β-3:4-dimethoxy-phenylpropionic acid. Veratraldehyde and mal-

onic acid were condensed in the presence of piperidine in pyridine solution, and the resultant 3:4-dimethoxy-cinnamic acid was reduced with sodium amalgam. (Haworth, Perkin and Pink, J.C.S., 1925, _127_, 1714.)

β-3:4-dimethoxy-phenylpropionamide. The preparation of this substance, for which various methods have been described in the literature, offers considerable difficulty. Buck and Perkin (J.C.S., 1924, _125_, 1679) passed dry ammonia through the molten acid at 220-230°C., and Haworth and Perkin (J.C.S., 1926, 1775) treated the acid with thionyl chloride in chloroform and then poured the reaction mixture into an aqueous solution of ammonia and sodium hydroxide. The latter process was carried out and yields varying between 30 and 40 per cent of the theoretical were obtained. A slight improvement was effected by the use of carbon tetrachloride instead of chloroform; the increase in yield was probably due to the fact that chloroform usually contains some alcohol whereas carbon tetrachloride does not. Eventually the method described by Child and Pyman (J.C.S., 1929, 2013) was employed. These authors have re-examined the various methods available and have come to the conclusion that the amide is best prepared from the ethyl ester. The ester, obtained in excellent yield by heating the acid under reflux with absolute ethyl alcohol

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φ 4: 5-Dimethoxy-2-β-methylaminoethyl-benzaldehyde (XI) has been so named; it is used in medicine. ~Translation~ 'δ.

in the presence of a small amount of sulphuric acid, was
shaken with concentrated ammonia for 4 days.   The ester
passed gradually into solution and was replaced by the pure
amide.

β-Veratrylethylamine. The amine was prepared by heating the
above amide with aqueous sodium hypo-chlorite solution.
(Buck and Perkin, J.C.S., 1924, 125, 1679).   The base was
converted to the hydrochloride by treatment with hydrogen
chloride in benzene solution.   (Mannich and Jacobsohn, Ber.,
1910, 43, 196.)

       Very high yields have been claimed for more direct
methods of preparing β-veratrylethylamine.   Kindler, (Arch.
Pharm., 1931, 269, 70) reduced 3:4-dimethoxy-acetyl-mandelo-
nitrile with hydrogen under 3-4 atmospheres pressure, and
Kondo and Kondo (Zent., 1928, ii, 55) obtained the base by
the electrolytic reduction of 3:4-dimethoxy-ω-nitrostyrene.
Unfortunately the apparatus necessary for the performance
of these experiments was not available, and an unsuccessful
attempt was made to reduce the nitrostyrene with sodium and
alcohol.

3:4-dimethoxy-ω-nitrostyrene.   Nitromethane was prepared
from chloracetic acid and sodium nitrite (Organic Synthesis,
vol. III, p. 83) and condensed with veratraldehyde according
to the procedure adopted by Lange and Hambourger in the

preparation of related compounds (J.Am.C.S., 1931, 53, 3865).
A solution of 7.5 grams veratraldehyde in 200 c.c.s, 95%
ethyl alcohol was cooled to 5°C., and to it were added 6 grams
nitromethane, 100 c.c.s of a 5% solution of sodium hydroxide
in alcohol, also at 5°C., were added to the mixture at the
rate of 5 c.c.s per minute; during the addition vigorous
stirring was maintained and the temperature was kept below
10°C.   Ice-water was now added until the sodium salt which
had separated just dissolved, and the resultant clear solu-
tion was poured into a mixture of 60 c.c.s concentrated hydro-
chloric acid and 90 c.c.s water.   After standing for half an
hour the precipitate was collected by filtration.   The yield
of 7 grams was equivalent to 75% of the theoretical.   The
m.pt., 142°C., was the same as that recorded by Kondo and
Kondo (ibid.)

12 grams sodium were added gradually to a solution of
7 grams ⍵-3-4-dimethoxy-nitrostyrene in 200 c.c.s ethyl
alcohol.   During the addition of the sodium an insoluble
tar was deposited, from which no basic product could be ex-
tracted.

2-Methyl-6: 7-dimethoxy-1:2:3:4-tetrahydroisoquinoline.

The method employed by Decker and Becker (Annalen, 1913, 395,
358) for the conversion of homo-piperonylamine to hydrohydra-
stinine was applied with equal success in this case. 5 grams
β-veratryl-ethylamine hydrochloride and 12 c.c.s formalin were
heated in a sealed tube at 150°C. for 2½ hours.   The product
was evaporated to dryness on the water bath, and the hydro-

chloride so obtained was recrystallised from a mixture of alcohol and ether, M.pt. 214°C. (cf. Pyman J.C.S., 1909, 95, 1270). The pure base was obtained by the addition of strong caustic soda solution to an aqueous solution of the hydrochloride. The melting point, 83-84°C, was the same as that recorded by Pyman (ibid.).

Oxidation of 2-methyl-6:7-dimethoxy-tetrahydroisoquinoline to 4:5-dimethoxy-2-β-methylaminoethyl-benzaldehyde.

According to Pyman (loc.cit.,p.1746) the above reaction takes place easily in cold dilute chromic acid; in the present case the desired product, isolated as 1-chloro-2-methyl-6:7-dimethoxy-tetrahydroisoquinoline, was obtained only in very small yield (20-25%), and other methods of oxidation were therefore attempted.

Pyman employed pyrolusite in his original experiments on the oxidation of laudanosine and obtained 4:5-dimethoxy-2-β-methylaminoethyl-benzaldehyde in good yield as one of the products. (loc.cit.,p.1269). The same method was tried unsuccessfully. The base was dissolved in 15% sulphuric acid and mixed with excess manganese dioxide; the mixture was stirred at 80°C for 12 hours. After filtration, neutralisation with sodium carbonate, and further filtration, the solution was made strongly alkaline with sodium hydroxide and extracted with ether. On evaporation of the solvent the starting material was recovered and identified after recrystallisation from petroleum ether, by its melting point and mixed melting point with the pure compound.

Oxidation with iodine was also unsuccessful, <u>1-keto-2-</u>
<u>methyl-6:7-dimethoxy-tetrahydroisoquinoline</u> (XXlll) being
produced.

(XXIII)
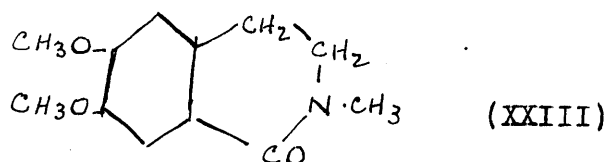
3·2 grams 2-methyl-6:7-dimethoxy-tetrahydroisoquinoline and
5·2 grams sodium acetate were dissolved in alcohol, and to
the gently boiling solution 5 grams iodine, dissolved in
alcohol, were added gradually. Heating was continued until
the iodine colouration was almost completely discharged and
then water was added and the alcohol removed by evaporation.
The aqueous solution was made alkaline and extracted with
ether. From the hydrochloric acid extract of the ethereal
solution 1.5 grams of a white solid were obtained on addition
of strong sodium hydroxide solution. This substance, after
recrystallisation from acetone, melted at 124-125°C. On
addition of 7.3 c.c.s. N/4 hydrochloric acid to 0.4 grams
of the compound it dissolved and almost immediately a white
solid separated. The latter melted at 40°C., and after
heating in the steam oven for several hours the melting point
was found to be 124-125°C.

According to Pyman (loc.cit.,p.1270.), 4:5-dimethoxy-
2- β -methylaminoethyl-benzaldehyde melts at 123-124°C, and
forms a chloride which is deposited from aqeous solutions as

a solid melting at 61-62°C; after drying at 100°C this substance melts at 186°C. Since the properties of the iodine oxidation product were not in agreement with these observations, it was assumed to be 1-keto-2-methyl-6:7-dimethoxy-tetrahydroisoquinoline which is described by the same authority as a weakly basic substance melting at 126°C., and forming an unstable hydrochloride. The low yield obtained was also in accordance with this assumption since it requires a very large amount of acid to extract the keto-compound from organic solvents. (Pyman, ibid.)

Buck's synthesis of 4:5-dimethoxy-2-β-methylaminoethyl-benzaldehyde (J. Am.C.S., 1930, 52, 4119) was repeated. It was practically identical with the foregoing synthesis up to the preparation of β-veratrylethylamine, thereafter the procedure was different. The benzylidene derivative of β-veratrylethylamine was prepared by mixing equimolecular quantities of the base and benzaldehyde, the water formed in the reaction being removed by heating under reduced pressure, and was mixed with an equivalent amount of methyl iodide and heated with careful exclusion of air and moisture for 20 hours at 37°C. The resulting yellow solid was boiled with 90% alcohol and on cooling N-methyl-β-veratrylethylamine hydriodide separated; the free base was obtained by addition of strong caustic soda to an aqueous solution of the hydriodide followed by extraction with benzene. The product was converted to N-formyl-N-methyl-β-veratrylethylamine by heating with

formic acid and the latter was heated with phosphorus pent-
oxide for 30 minutes after which the reaction mixture was
poured into water. After filtration and addition of strong
caustic soda, 4-5-dimethoxy-2-β-methylaminoethyl-benzaldehyde
was extracted with benzene from the aqueous solution and con-
verted immediately to 1-chloro-2-methyl-6: 7-dimethoxy-tetra-
hydroisoquinoline by extracting the benzene solution with
hydrochloric acid; the chloride was isolated by evaporating
the acid solution to dryness on the water bath.

1-Cyano-2-methyl-6: 7-dimethoxy-tetrahydroisoquinoline. The
nitrile was prepared by adding an aqueous solution of potas-
sium cyanide to a solution of the above chloride in water.
(Pyman, J.C.S., 1909, 95, 1272.)

Experiments with 1-Cyano-2-methyl-6: 7-dimethoxy-tetrahydro-
    isoquinoline and methyl magnesium iodide.

    1.3 grams nitrile, dissolved in 200 c.c.s, anhydrous
ether, were added slowly to 3 times the theoretical quantity
of methyl magnesium iodide cooled in ice and salt, and allowed
to stand for 15 hours. The mixture was warmed for a short time
on the water bath and then ice and ammonium chloride were added.
The ether layer was separated, washed with water and dried
over potassium carbonate. Picric acid, dissolved in ether,
was added to a sample of the ether solution and a yellow
picrate separated. The melting point of this substance (A)
was 160°C. Now, inactive Carnegine picrate has been reported
as melting at 212-213°C. (Späth and Kuffner, Ber., 1929, 62,
2242.), and the picrate of the original nitrile (B), prepared

in ether, was found to melt at 163°C. The mixed melting point of (A) and (B) was 160°C. The presence of unchanged nitrile was confirmed by the recovery of the starting material. The remainder of the ether solution was extracted many times with hydrochloric acid and the total acid solution was evaporated to dryness on the water bath. The residue was redissolved in water and to the solution an aqueous solution of potassium cyanide was added. The nitrile was deposited; it was identified by its melting point and mixed melting point with the pure compound.

In the above experiment a large volume of ether was used because of the low solubility of the nitrile in that solvent, and it was thought that the negative result might be due to the low concentration of the reactants. The experiment was repeated using 30 c.c.s ether and on this occasion the nitrile was added in the form of a fine powder. The mixture was warmed on the water bath and stirred for 6 hours. The presence of unchanged material was detected and confirmed as above; no other basic produdts could be isolated from the ether layer.

A further modification was employed. Methyl magnesium iodide was prepared in the usual manner, and then toluene, previously distilled over sodium, was added. After the excess ether had been distilled off the finely ground nitrile was added, and the mixture was heated under reflux for 8 hours. Again no reaction took place.

PART II.

α-Cyano-N-methylpyrrolidine.

(A)

Allyl Bromide was prepared by the action of Hydrobromic acid upon allyl alcohol. (Organic Synthesis, vol. I, p.3.)

Trimethylene bromide. Allyl bromide was saturated with dry hydrogen bromide and then exposed to sunlight; this process was repeated until no more hydrogen bromide was absorbed. (Bruylants, Rec. d. Trav. Chim. d. Pays-Bas. 1909, 28, 240.)

γ-Bromopropyl-cyanoacetic ester. 23 grams cyanocetic ester and 44 grams trimethylene bromide, both of which were freshly distilled, were dissolved in 45 grams anhydrous ether, and to the mixture was added a cooled solution of 4.6 grams sodium in 46 grams absolute ethyl alcohol. On frequent shaking during which the liquid became slightly warm, sodium bromide began to separate. The mixture was allowed to stand for 36 hours at room temperature and then was shaken with dilute hydrochloric acid. The ether layer was separated, washed several times with water and dried over sodium sulphate. After evaporation of the ether the product was fractionated; 3 grams γ-bromopropyl-cyanoacetic ester, b. pt. 173-175°C. under 18 m.m. pressure, were obtained along with a lower fraction, consisting mainly of unchanged trimethylene bromide and cyanoacetic ester, and a considerable quantity of non-volatile gum.

The low yield obtained in this instance is comparable

with that reported by Willstätter and Ettlinger (Ann.1903, 326, 99) in the preparation of γ-bromopropyl-malonic ester by the condensation of malonic ester and trimethylene bromide; they obtained 63 grams crude product from 160 grams malonic ester.

Attempted hydrolysis of γ-bromopropyl-cyanoacetic ester.

The ester which was insoluble in water, was mixed with dilute hydrochloric acid; after stirring the mixture at 60°C for eight days none of the ester had passed into solution. The acid layer was separated and extracted with ether. On evaporation of the ether, after drying over sodium sulphate no product was obtained.

The low yield of the ester obtained in the condensation, coupled with the apparent difficulty in converting the ester to the acid made the process impracticable and it was therefore abandoned.

(B).

Allyl chloride. was satisfactorily prepared by heating a mixture of crude allyl alcohol (1 mol.) and strong hydrochloric acid (300 c.c.s) on the water bath, the product being distilled off through a column as it was formed. The distillate was washed with water, dried over calcium chloride and then fractionated (column). B.pt 46°C.

Trimethylene chlorobromide. This substance was obtained by a modification of the method described by Bruylants (ibid.) Allyl chloride was placed in a quartz flask and saturated

at 0°C. with dry hydrogen bromide which was obtained by dropping bromine on gently boiling tetrahydronaphthalene. The mixture was then exposed to the ultra-violet rays of a mercury vapour lamp for about an hour after which the liquid was again saturated with hydrogen bromide and exposed. This process was repeated until no further solution of hydrogen bromide, as indicated by gain in weight, was observed. The product was washed with water and dried with calcium chloride. It was then fractionated. B.pt., $142\text{-}144^{\circ}$C. Yields over 80% of the theoretical were obtained.

The observation that exposure to ultra-violet light causes a considerable increase in yield has been confirmed in a paper on the preparation of trimethylene chlorobromide published since this work was carried out. In this case the reaction mixture was exposed to strong sunlight; yields as high as 97% are claimed (Strukov, Khim. Farm. Prom,1933, 2, 66-8.).

ɣ-Chloro-butyronitrile was prepared by the action of potassium cyanide upon trimethylene chlorobromide in a mixture of alcohol and water. (Organic Synthesis, vol.VIII., p.52)

Attempted preparation of ɣ-chloro-butyraldehyde.

These experiments were based upon a general method for the preparation of aldehydes from nitriles described by Stephen. (J.C.S., 1925, 127, 1874.)

Anhydrous stannous chloride was prepared by heating the pure

crystalline variety until the temperature rose to 180°C.

50 grams anhydrous stannous chloride were suspended in 200 c.c.s ether previously distilled over sodium, and dry hydrogen chloride was passed into the suspension until the salt was completely dissolved with formation of two layers. 15 grams γ-chlorobutyronitrile were added gradually with vigorous shaking. At this point a crystalline aldimine stannichloride should have separated, but in the present case no such separation was observed, and no apparent change was brought about by gentle heating. The ether was evaporated off and the stannous chloride was dissolved in water; the resultant mixture was extracted with ether, from which, after washing with water and drying over calcium chloride, unchanged nitrile was recovered.

The period of contact of the reactants was increased, but even after standing for 10 weeks no aldimine stannichloride separated. Unchanged nitrile was recovered as above.

<u>γ-Methylamino-butyronitrile</u>. An attempt was made to prepare the methylamino-nitrile for the purpose of subjecting it to the above treatment. Equivalent quantities of γ-chlorobutyronitrile, monomethylamine hydrochloride and sodium methoxide were heated in methyl alcoholic solution at 55-60°C for 2 hours. The alcohol was then distilled off and water was added to the residue. The mixture was made alkaline and extracted with ether from which, after washing and drying, γ-chlorobutyronitrile was recovered unchanged.

(C)

β-Bromopropionaldehyde diethylacetal was conveniently prepar-
ed in the following manner.

200 c.c.s ethyl alcohol, cooled in ice and salt,
were saturated with dry hydrogen bromide. To the saturated
solution 80 grams acrolein, also cooled to $0^{o}C.$, were added
gradually and the mixture was allowed to stand for 12 hours
after which it was neutralised with calcium carbonate. After
filtration the product was washed with water and dried over
potassium carbonate. The yield was 172 grams. No further
purification was attempted.

γ-Amino-butyraldehyde diethylacetal. β-Cyanopropionaldehyde
was prepared and reduced in one operation. The experiment
described below was adapted from the process described by
Wohl, Schäfer and Thiele. (Ber., 1905, 38, 4157.)

The product obtained from the previous stage was
dissolved in 600 c.c.s alcohol and to the solution were
added 90 grams finely powdered sodium cyanide and 10 grams
sodium iodide. The mixture was heated under reflux and
stirred for 24 hours, and then a further quantity of alcohol
(1,700 c.c.s) was added. 150 grams sodium were added so as
to keep the mixture boiling gently and when the addition was
complete the mixture was boiled vigorously for 3 hours.
After addition of $1\frac{1}{2}$ litres of water the alcohol was dis-
tilled off and the residue was extracted with ether.

After drying over potassium carbonate and subsequent removal
of the solvent, the product was fractionated under reduced
pressure.   Yield 65 grams. B. Pt. 96-100°C., under 19 m.m.
pressure.

Attempted hydrolysis of the acetal.   The acetal was heated
gently with excess dilute hydrochloric acid on the water bath;
the solution became dark brown in colour. On cooling the solu-
tion was saturated with potassium carbonate and extracted with
ether. The ether solution was dried over potassium carbonate
and reduced in bulk, and on addition of methyl iodide only a
very small quantity of oily material separated.

An attempt was made to hydrolyse the acetal by the
method described by Wohl, Schäfer and Thiele (ibid.) These
authors did not describe the free aldehyde and stated that
they were unable to prepare the oxalate of γ-aminobutyralde-
hyde in a pure state.

30 grams γ-aminobutyraldehyde diethylacetal were dis-
solved in a solution of 36 grams oxalic acid in 300 c.c.s
water and heated gently for a few moments. The solution was
allowed to stand for 36 hours. Potassium carbonate was then
added and the mixture was extracted with ether. After drying
over potassium carbonate and removal of the solvent the product
was fractionated under reduced pressure. 10 grams acetal were
recovered along with a small quantity of material boiling above
200°C. under 17 m.m. pressure and a considerable quantity of
non-volatile gum.

SUMMARY.

PART I.

(1) 1-Cyano-2-methyl-6: 7-dimethoxy-1: 2: 3: 4 tetra-hydroisoquinoline was synthesised starting from vanillin. The synthesis provides an alternative, but somewhat less efficient, method to Buck's synthesis of 4: 5-dimethoxy-2-β-methylamino-ethyl-benzaldehyde. This substance was obtained in the present case by converting β-veratrylethylamine to 2-methyl-6: 7-dimethoxy-1: 2: 3: 4 tetrahydroisoquinoline which was then oxidised to the aldehyde. Buck also employed β-veratrylethyl-amine but he first prepared the formyl derivative of the methylated base which he then converted to the aldehyde by treatment with phosphorus pentoxide etc..

(2) On oxidation with iodine 2-methyl-6: 7-dimethoxy-1: 2: 3: 4-tetrahydroisoquinoline gives 1-keto-2-methyl-6: 7-dimethoxy-1: 2: 3: 4-tetrahydro-isoquinoline.

(3) The above nitrile does not react with methyl magnesium iodide and the syntheses of Carnegine and Laudanosine had to be abandoned.

(4) 3-Methoxy-4-benzyloxy-benzyl alcohol, 3-methoxy-4-benzyloxy-benzoic acid and 3-methoxy-4-benzyloxy-benzyl chloride have been prepared and described. The halide appears only to form a Grignard reagent with difficulty.

(5) 3-4-Dimethoxy-ω-nitrostyrene cannot be reduced with sodium and alcohol.

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PART II.

Three schemes for the preparation of α-cyano-N-methylpyrrolidine have been investigated; in all cases negative results were obtained.

(A) Trimethylene bromide and sodio-cyanoacetic ester were condensed to give γ-bromopropyl-cyanoacetic ester; the yield was very poor. An unsuccessful attempt was made to hydrolyse the ester to γ-bromopropyl-cyanoacetic acid.

(B) γ-Chlorobutyronitrile was prepared from allyl alcohol, but it could not be converted to γ-chlorobutyraldehyde via the aldimine stannichloride.

Stephen's method for the preparation of aldehydes from nitriles appears not to be of much value with the lower aliphatic compounds.

(C) γ-Aminobutyraldehyde diethylacetal was obtained from acrolein. Efforts to prepare the free aldehyde were unsuccessful.


THE REDUCTION OF α-AMINO-NITRILES.


DISCUSSION.

It has been known for some time that sodium and benzaldehyde react without evolution of hydrogen, and in 1924 Blicke prepared and investigated the addition compounds formed when these substances are mixed in anhydrous ether.[24] In addition to determining the conditions under which each of these compounds is formed, he was able to establish their constitutions by a study of their reactions. To the compound formed when one molecule of benzaldehyde is treated with two atoms of sodium, benzaldehyde disodium, he gave the formula:-
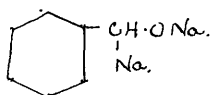

It was thought that the double decomposition reaction of Grignard reagents and α-amino-nitriles (see p.54),
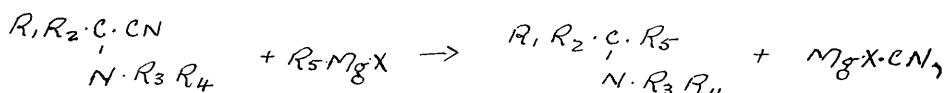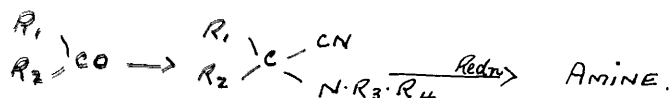

might be extended to such disodium derivatives of aldehydes, thus providing a method for the synthesis of compounds of the adrenaline type. For example adrenaline itself might be prepared from piperonal disodium and methylamino-acetonitrile by the following stages,
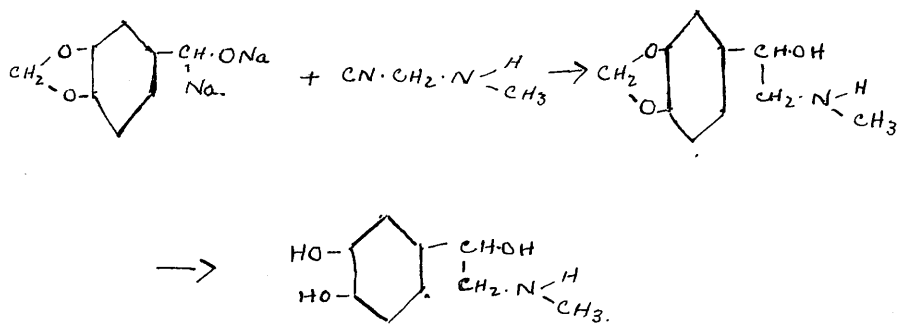
In the course of a preliminary experiment with benzaldehyde disodium and α-dimethylamino-n-butyro-nitrile in dry ether, a considerable quantity of dimethyl-n-propylamine was produced. This reduction of the nitrile must have been caused by unchanged atomised sodium mixed with the disodium compound; the hydrogen produced by the action of the sodium on part of the nitrile no doubt served to reduce a further portion. This replacement of the cyano-group by hydrogen when sodium acts upon a nitrile has been observed quite often. The researches of Ernst von Meyer and others have shown that ethane is one of the products when propionitrile is treated with sodium in anhydrous ether,[25] and Rising and Braun have recently proved that toluene, sodium cyanide and the sodium salt of benzyl cyanide are produced in equimolecular amounts when benzyl cyanide is treated with sodium in the absence of moisture.[26]
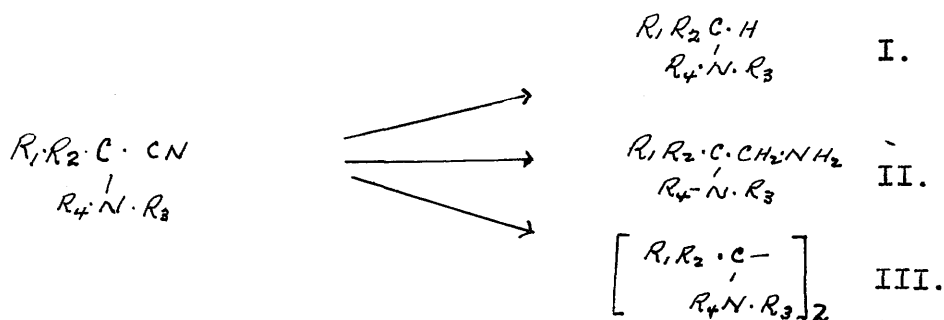
$$2\ C_6H_5 \cdot CH_2 \cdot CN\ +\ 2\ Na\ \longrightarrow\ (C_6H_5 \cdot CH \cdot CN)Na\ +\ NaCN\ +\ C_6H_5 \cdot CH_3.$$
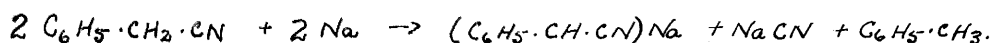
The important point in the present instance was the apparent ease with which α-dimethylamino-n-butyronitrile was reduced. An examination of the literature showed that only in isolated cases have α-amino-nitriles been employed in the preparation of amines by reduction, and since these nitriles are usually fairly easily obtained from aldehydes and ketones, it was decided to study the reduction of a number of these compounds in order to test the preparative utility of the following route,

$$\frac{R_1}{R_2} \Big\rangle CO\ \longrightarrow\ \frac{R_1}{R_2}\Big\rangle C \Big\langle \begin{array}{c} CN \\ N \cdot R_3 \cdot R_4 \end{array} \xrightarrow{\text{Redn}}\ Amine.$$

Meanwhile the original line of investigation has been abandoned. There can be little hope of success in these experiments until some suitable technique is developed for the complete separation of the very unstable, insoluble benzaldehyde disodium compound and unchanged sodium, or until some soluble dimetallic derivative is discovered.

As several of the conventional reducing agents proved unsatisfactory, a modification of the original experiment was carried out. The nitrile was dissolved in slightly moist ether and added gradually to atomised sodium (method (1)); moderate yields were obtained in the three cases tried, although the reaction was too violent for easy manipulation. Better restults were obtained by adding sodium in slices to the nitrile dissolved in ether floating on potassium bicarbonate (method (2)). These two very similar processes did not always lead to the same result.

As in the interaction of α-amino-nitriles and the Grignard reagent (cf. p. 5%.), three types of product are formally possible when the cyano group of an α-amino-nitrile is reduced. The cyano group may be replaced by hydrogen (I), or it may be reduced <u>in situ</u> to $CH_2.NH_2$ (II); or it may be removed, the nitrile undergoing a Fittig-Wurtz reaction (III).

$$R_1R_2C \cdot CN \quad\quad \begin{cases} R_1R_2C \cdot H \\ \quad | \\ R_4 \cdot N \cdot R_3 \end{cases} \text{I.}$$

$$R_4 \cdot N \cdot R_3$$

$$\begin{matrix} R_1R_2 \cdot C \cdot CH_2 \cdot NH_2 \\ \quad | \\ R_4 \cdot N \cdot R_3 \end{matrix} \text{II.}$$

$$\left[\begin{matrix} R_1R_2 \cdot C - \\ \quad | \\ R_4 \cdot N \cdot R_3 \end{matrix} \right]_2 \text{III.}$$

Reactions of types I and II have been observed in these reduction experiments, but no Fittig-Wurtz synthesis has been encountered. It may be remarked here that most of the researches previously carried out have been concerned with the reduction of the CN-group to $Ch_2.NH_2$, as in the reduction of benzyl cyanide to β-phenyl-ethylamine,[27] and examples such as the reduction of p-aminobenzyl cyanide to p-toluidine have been regarded as 'abnormal.'[28]

The results are summarised in Table I. The three nitriles reduced by method (1) gave products of type I; on reduction by method (2) two of these, α-dimethylamino-n-butyronitrile (A) and α-dimethylamino-isobutyronitrile (B), gave products of type II, while in the other, α-dimethylamino-phenyl-acetonitrile (F), the cyano-group was again replaced by hydrogen.
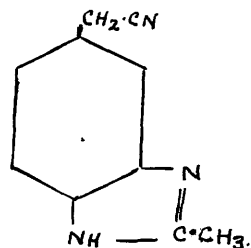
Table I.

	$R_1 . R_2 . C . CN . N . R_3 R_4$			Method (1)		Method (2)	
	R_1	R_2	R_3	R_4	Product	Yield %	Product	Yield %
A	C_2H_5	H	CH_3	CH_3	I	30-40	II	39
B	CH_3	CH_3	CH_3	CH_3	I	30-40	II	22
C	CH_3	CH_3	H	H			Decomp.	-
D	CH_3	H	C_6H_5	C_2H_5			II	55
E	CH_3	H	$>C_5$	H_{10}			II	25
F	C_6H_5	H	CH_3	CH_3	I	50	I	57
G	C_6H_5	H	$>C_5$	H_{10}			I	85
H	C_6H_5	H	CH_3	H			I	19ø
I	C_6H_5	H	H	H			I	46
K	C_6H_5	H	C_6H_5	CH_3			I	50
L	C_6H_5	CH_3	C_6H_5	H			I	55

ø. Calculated on the crude nitrile, which cannot be purified.

These two types of reduction have already been encountered by Purgotti who reduced α-amino-phenylacetonitrile to phenylethylenediamine (type II) with zinc and hydrochloric acid;[29] and by Gulewitsch and Wasmus who obtained a little isopropylamine (type I) by reducing α-amino-isobutyronitrile with sodium and alcohol.[30] Products of type I have also been reported by Bloch in the reduction of 5-cyanomethylbenziminazole (XXXIV) and 5-cyanomethyl-2-methylbenziminazole (XXXV), which are δε-diamino nitriles, to 5-methylbenziminazole and 2:5-dimethylbenziminazole, respectively, with sodium and alcohol.[27] Considered, along with the results obtained in the reduction of the butyronitriles (A) and (B), these suggest that replacement of the cyano-group by hydrogen (type I) is favoured by alkaline conditions, whereas reduction of the CN-group to $CH_2.NH_2$ (type II) is favoured by acids.
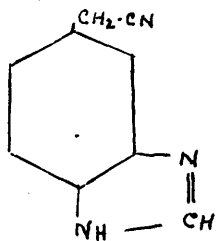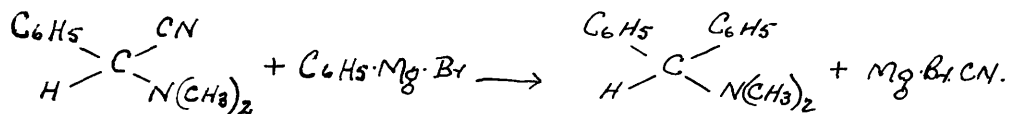

XXXIV.   XXXV.

The results obtained by reduction over potassium bicarbonate (method (2)) are interesting. Reference to Table I will show that replacement of the cyano-group by hydrogen (type I) appears to occur only with those nitriles which have a phenyl group attached to the α-carbon atom, i.e. only where R_1 or R_2 is a phenyl radical, otherwise the nitrile group is not

replaced but reduced <u>in situ</u> (type II). Phenylation of the

nitrogen has no effect as can be seen from the case of α-

ethylanilinopropionitrile (D), which was reduced to α-amino-β-

ethylanilinopropane. These results may be compared with those

obtained by Thomson and Stevens in the interaction of α-di-

methylamino-nitriles and the Grignard reagent (see p. 5%).

In reduction by method (2), α-phenylation of the nitrile

causes replacement of the cyano-group by hydrogen, while in

the Grignard reaction the presence of a phenyl group in the

α-position leads to suppression of the normal reaction of

ketone formation in favour of the displacement of the nitrile

group by the radical of the Grignard reagent. e.g.,

$$\underset{H}{\overset{C_6H_5}{>}}C\underset{N(CH_3)_2}{\overset{CN}{<}} + C_6H_5\cdot Mg\cdot Br \longrightarrow \underset{H}{\overset{C_6H_5}{>}}C\underset{N(CH_3)_2}{\overset{C_6H_5}{<}} + Mg\cdot Br\cdot CN.$$

As a means of preparing amines from aldehydes and

ketones, the reduction of α-amino-nitriles compares quite

favourably with the other available processes. The reduction

of such carbonyl derivatives as oximes and phenylhydrazones

can be employed only in the preparation of primary amines,

and only secondary amines can be obtained by the reduction of

Schiff's bases, e.g., benzylaniline from benzalaniline,

$$C_6H_5\cdot CH = N\,C_6H_5 \quad \longrightarrow \quad C_6H_5\cdot CH_2\cdot NH\cdot C_6H_5$$
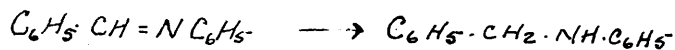
The scope of the latter process is further limited by the

fact that aromatic aldehydes constitute the sole class of

carbonyl compounds from which Schiff's bases can be prepared

satisfactorily. The Leuckart-Wallach method for the conver-

sion of aldehydes and ketones to amines,[31] in which a mixture

of aldehyde or ketone, formic acid, and amine is heated in
a sealed tube at about 200°C., gives varying results. In some
cases excellent yields are obtained, e.g., the preparation
of benzyl-piperidine from benzaldehyde, formic acid, and
piperidine,

$$C_6H_5.CHO + H.CO.OH + HN:C_5H_{10} \longrightarrow C_6H_5CH_2.N.C_5H_{10} + H_2O + CO_2;$$
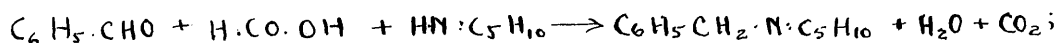
in others the desired amine is obtained mixed with its formyl
derivative; and in others the method has been found to be of
little value. Recently Skita and his collaborators have suc-
cessfully alkylated amines by the hydrogenation of a mixture
of aldehyde or ketone and amine,[32] e.g., they have prepared N-
ethyl-isoamylamine from acetaldehyde and iso-amylamine, and
also from isovaleraldehyde and ethylamine; attention has been
mainly concentrated on the alkylation of secondary amines,
but the method cannot be regarded as of general application
since the yields are greatly reduced if the amine has a branch-
ing in the carbon chain, or a phenyl group, near the nitrogen
atom, and only ketones containing a -CO.CH$_3$ group give good
yields.

The violence of the reaction makes the reduction of
α-amino-nitriles in moist ether with atomised sodium imprac-
ticable, but those nitriles which have a phenyl group attached
to the α-carbon atom can be converted to monamines in good
yield by reduction with sodium over potassium bicarbonate
(method (2)); the method can be employed for the preparation
of primary, secondary, and tertiary amines (see Table I). Ow-
ing to the large amount of sodium employed in the reduction,

and to the instability of the nitriles in the presence
of moisture (see Experimental part, p. 47.), the method
does not lend itself to the treatment of large quantities.

EXPERIMENTAL.

The original experiment with benzaldehyde disodium (Blicke, J. Am. C.S., 1924, __46__, 2560) and α-dimethylamino-n-butyronitrile (A) was carried out in the following way. Sodium (1.7 grams) was atomised under boiling toluene, and, after cooling, anhydrous ether was added. The required inert atmosphere was obtained by distilling off some of the ether and closing the apparatus immediately the source of heat was removed. Freshly distilled benzaldehyde (4 grams) was then added slowly, shaking being maintained during the addition; the deep green, insoluble addition compound was formed. After standing for some time the nitrile (4 grams) was introduced; at this point a brisk reaction took place. The mixture was allowed to stand at room temperature for two days after which alcohol and then water were added; on addition of the alcohol the mixture turned dark blue in colour, and when the water was added a deep red colouration was developed. The ether layer was separated, and the basic products were extracted from it by shaking with dilute hydrochloric acid. The acid was separated, neutralised, and extracted with ether. The ether was dried over potassium carbonate, and on addition of picric acid dissolved in ether, a yellow picrate was obtained. After recrystallisation from alcohol this substance melted at 108-109°C., and its mixed melting point with authentic dimethyl-n-propylamine picrate was also 108-109°C. (Hanhart and Ingold, J.C.S., 1927, 1007.) The nitrile had therefore been reduced

to dimethyl-n-propylamine. The unstable nature of the disodium compound coupled with its insolubility in suitable solvents makes its separation from unchanged sodium practically impossible; moreover the larger particles of sodium become coated with the addition compound leaving a metallic core. The use of excess of the aldehyde is, of course, impossible in view of the formation of the monosodium compound (XXXVI) (cf. Blicke, loc. cit.).

$$-\overset{\cdot}{C}H\cdot ONa.$$

XXXVI.
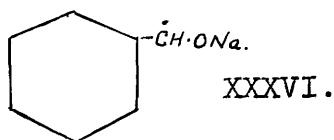
It was found convenient to prepare most of the following nitriles by addition of amine hydrochloride in water to a mixture of aldehyde or ketone and potassium cyanide in water, or by addition of acetic acid to a mixture of aldehyde or ketone, amine, and potassium cyanide in water; the yields obtained by this method were satisfactory. In the preparation of low melting, solid nitriles the reactants were mixed at $0^{\circ}C.$, and the crude product then needed no further purification, though this procedure caused a diminution in yield. The known compounds had the properties ascribed to them by the authorities cited.

Some preliminary reduction experiments were carried out with α-dimethylamino-phenylacetonitrile (F). The nitrile was heated with excess zinc and acetic acid. When the zinc was completely dissolved, water and excess sodium hydroxide solution were added, and the resultant alkaline mixture

was extracted with ether. Ethereal picric acid was added
to the dried ether and dimethylamine picrate separated and
was identified by its melting point and mixed melting point
with an authentic specimen - 157°C. The yield indicated
that most of the nitrile had been decomposed during the ex-
periment. Similar results were obtained in attempted reduc-
tions with aluminium amalgam and alcohol, sodium amalgam and
alcohol, and sodium and alcohol. In each case the nitrile
was treated with a large excess of the reducing agent, and
when the reaction had ceased, water and hydrochloric acid
were added to the mixture and the alcohol was distilled off
through a column. In the case of aluminium amalgam the
reaction mixture was filtered and the residue of aluminium
hydroxide washed thoroughly with alcohol before addition of
acid. The acid solutions were then made alkaline with sod-
ium hydroxide and extracted with ether from which dimethyl-
amine was again isolated as picrate. Since these attempts
were unsuccessful, modifications of the original experiment
were tried.

Method (1).

The nitrile (1 mol.), dissolved in slighly moist
ether, was added gradually to sodium (5-6 atoms), previously
atomised under toluene. The reaction was extremely violent,
and when it had subsided alcohol and water were added. The
ether layer was separated and dried over potassium carbonate,
and then the ether was distilled off through a column, giving

the 'distillate' and 'residue' referred to below.

The replacement of moist ether by ether containing alcohol led to no improvement; a moderate excess of alcohol, calculated on the amount of sodium used, was mixed with the ether in which the nitrile was dissolved.

Method (2).

The nitrile (1 mol.) was dissolved in ether and placed over a strong solution of potassium bicarbonate (20 mols.), sufficient ether being used to provide a layer of suitable depth. Sodium (20 atoms) was added in the form of thin slices, and the reduction was conducted so as to maintain gentle ebullition. When the addition was complete the ether was separated and treated as in (1). In both methods water soluble bases were salted out by potassium carbonate before separation of the ether.

Since fairly small quantities of the nitriles were employed (the difficulty in manipulation in method (1), and the comparatively large quantities of sodium required in method (2) made small amounts of starting materials desirable), it was found convenient to isolate and identify the products as salts; picrates were usually prepared, although for analytical purposes hydrochlorides sometimes proved more suitable. The former were obtained by adding picric acid. dissolved in ether, to an ethereal solution of the product, while the latter were prepared by passing dry hydrogen chloride through a dry ethereal solution of the product. The percentage picric

acid, or hydrogen chloride, in these salts was estimated by titration in ethyl alcohol with alcoholic potash, phenolphthalein being used as indicator.

(A) α-Dimethylamino-n-butyronitrile was prepared in good yield by addition of acetic acid to a mixture of propionaldehyde, dimethylamine, and potassium cyanide. It is a colourless liquid boiling at 156-158°C. The picrate was prepared in ether, and was obtained as small yellow prismatic needles which melted and decomposed at 148°C., after turning darker in colour at 142°C.

Analysis: Found $C_6H_3O_7N_3 = 67.2\%$

$C_6H_{12}N_2, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3 = 67.1\%$

In an attempt to recrystallise this compound it was dissolved in boiling alcohol; on cooling dimethylamine picrate separated (m.pt. and mixed m.pt. 157°C.). This is in accordance with the observations of Cocker, Lapworth, and Walton, who have reported that attempts to recrystallise α-diethylamino-propionitrile picrate led to a lowering of the melting point; the nitrile itself decomposed in the presence of moisture. (J.C.S., 1930, 440). This instability of α-amino-nitriles in the presence of moisture provided another reason for confining the reductions by method (2) to a small scale, since the treatment of larger quantities would have necessitated prolonged contact of the nitrile and the aqueous bicarbonate layer during the addition of the sodium.

(1) On reduction of the nitrile (4 grams) with sodium (4 grams) according to method (1), the 'distillate' gave

4.5 grams <u>dimethyl-n-propylamine picrate</u>, m.pt. and mixed
m.pt. 108-109°C. (Hanhart and Ingold, J.C.S., 1927, 1007.),
together with a trace of dimethylamine picrate.

(2) The nitrile(2.4 grams) was reduced with sodium
(10 grams) over a solution of 43 grams potassium bicarbonate
in water (method (2)). The 'distillate' gave no picrate on
addition of ethereal picric acid. From the 'residue' there
was obtained α-amino-β-dimethylamino-butane picrate (4.8
grams); on recrystallisation from acetone it was obtained
as fine yellow needles, m.pt. 176°C. (decomp., a change was
observed at 170°C.) This picrate is only slightly soluble
in alcohol, but is easily soluble in acetone. Attempts to
estimate the percentage picric acid by titration in acetone
solution with standard alcoholic potash were unsuccessful
because no sharp colour change could be observed in that
solvent; upon no occasion was acetone found to be a suitable
medium for such estimations. The <u>dihydrochloride</u> was there-
fore prepared and recrystallised from alcohol; it was a slight-
ly deliquescent substance melting at 169°C.
Analysis: Found HCl = 38.2%

$C_6H_{16}N_2$, 2HCl requires HCl = 38.6%

(B) α-<u>Dimethylamino-isobutyronitrile</u> (Henry and Dewael, Bull.
Acad. roy. Belg., 1904, 741) was easily prepared from dimethyl-
amine hydrochloride, acetone, and potassium cyanide in water.
(1) The nitrile (5 grams) was reduced with atomised
sodium (5 grams) according to method (1). The distillate

gave 5.65 grams <u>dimethylisopropylamine picrate</u>, m.pt. 240-241°C. (decomp.) (Thomson and Stevens, J.C.S., 1932, 2607)

Analysis: Found $C_6 H_3 O_7 N_3 = 42.4\%$

    Calculated for $C_5 H_{13} N, C_6 H_3 O_7 N_3$, $C_6 H_3 O_7 N_3 = 42.5\%$

    (2) The nitrile (2.5 grams) was placed over a solution of 44 grams potassium bicarbonate in water and reduced by addition of sodium (10 grams). The distillate gave no picrate. The residue yielded 2.80 grams α-amino-β-dimethyl-<u>amino-β-methyl-propane picrate</u>; it separated as fine yellow needles from a mixture of alcohol and acetone, m.pt. 184°C., and was found to be easily soluble in acetone, but only slightly soluble in alcohol. <u>The dihydrochloride</u> was obtained as a slightly deliquescent, white crystalline substance, m.pt. 256-258°C. after recrystallisation from alcohol.

Analysis: Found $HCl = 38.5\%$

    $C_6 H_{16} N_2, 2HCl$ requires $HCl = 38.6\%$

(C) <u>α-Amino-isobutyronitrile</u> (Gulewitsch and Wasmus, Ber., 1906, <u>39</u>, 1184) was prepared in the usual manner from acetone, potassium cyanide, and ammonium chloride.

    After reduction of the nitrile (5 grams) with 25 grams sodium over 118 grams potassium bicarbonate dissolved in water (method (2)), no picrate could be isolated from the distillate or residue. Since the nitrile decomposed fairly rapidly on standing, it probably did so under the experimental conditions, the basic products escaping (See A).

(D) α-Ethylanilino-propionitrile was obtained by mixing ethylaniline hydrochloride, potassium cyanide, and acetaldehyde in water; the yield was poor. It was obtained as a slightly yellowish liquid, b.pt. 133-134°C. under 10 m.m. pressure.

Analysis: Found: nitrogen = 16.2%

$\qquad$ $C_{11}H_{14}N_2$ requires nitrogen = 16.1%

10 grams sodium and 114 grams potassium bicarbonate were employed in reducing 3.8 grams nitrile. On working up in the usual manner the residue gave α-amino-β-ethylanilino-propane picrate (7.6 grams) which was recrystallised from a mixture of acetone and alcohol when it was obtained as yellow prisms, m.pt. 164°C. It was fairly soluble in acetone, but much less soluble in alcohol. The dihydrochloride melted at 199-200°C. after recrystallisation from alcohol.

Analysis: Found HCl = 29.4%

$\qquad$ $C_{11}H_{18}N_2, 2HCl.$ requires HCl = 29.1%

(E) α-Piperidino-propionitrile (Knoevenagel, Ber., 1904, **37**, 4086) was prepared by addition of acetic acid to a mixture of acetaldehyde, potassium cyanide, and piperidine in water.

The nitrile (4 grams) was reduced according to method (2), 13.5 grams sodium and 58 grams potassium bicarbonate being employed. From the residue 4.3 grams α-amino-β-piperidino-propane dipicrate were isolated; after recrystallis-ation from acetic acid this compound melted at 215°C. (decomp., change at 205°C.) It was only slightly soluble in acetone,

methyl alcohol, and ethyl alcohol.

Analysis: Found C. = 40.25%;   H. = 4.18%

$$C_8 H_{18} N_2 (C_6 H_3 O_7 N_3)_2 \text{ requires } C = 40\%; \ H. = 4.0\%$$

(F) α-Dimethylamino-phenylacetonitrile (Stevens, Cowan, and
MacKinnon, J.C.S., 1931, 2568) was prepared in good yield
from benzaldehyde, potassium cyanide, and dimethylamine
hydrochloride.

(1) 4 grams atomised sodium were used in reducing
5 grams nitrile according to method (1). Traces of dimethyl-
amine picrate were obtained from the distillate; it was
identified by its m.pt. and mixed m.pt. - 157°C. From the
residue there was isolated benzyl-dimethylamine picrate
(5.7 grams), m.pt. and mixed m.pt. with an authentic spec-
imen, 94°C.

(2) The following quantities were employed in a
reduction according to method (2): 5 grams nitrile, 14
grams sodium, and 60 grams potassium bicarbonate. No pic-
rate was obtained from the distillate. Since a very impure
product was produced in a preliminary experiment the residue
was steam distilled, and from the ether extract of the dis-
tillate benzyldimethylamine was isolated as picrate, m.pt.
and mixed m.pt. 94°C. Yield = 6.5 grams.

(G) α-Piperidino-phenylacetonitrile (Knoevenagel, ibid.)
was prepared from piperidine, benzaldehyde, potassium cyanide
and acetic acid; the preparation was performed at 0°C.

The nitrile (5 grams) was reduced according to method (2); 11.5 grams sodium and 50 grams potassium bicarbonate were used. When the addition of sodium was complete the ether layer was separated and washed thoroughly with water to remove any piperidine which might have been formed during the reaction; it was then dried over potassium carbonate. It yielded 8.6 grams N-Benzyl-piperidine picrate which separated from acetone as stout yellow prisms, m.pt. 176-177°C.

Analysis: Found $C_6 H_3 O_4 N_3 = 57.4\%$

$C_{12} H_{14} N, C_6 H_3 O_4 N_3$ requires $C_6 H_3 O_4 N_3 = 56.7\%$

The phenacylobromide was also prepared; it melted at 135-138°C. (slight effervescence) and the m.pt. remained unaltered on mixing with an authentic specimen (Stevens, J.C.S., 1930, 2117).

(H) α-Methylamino-phenylacetonitrile (von Miller and Plöchl, Ber., 1898, **31**, 2717) was prepared from benzaldehyde, potassium cyanide, and methylamine hydrochloride; it was obtained mixed with a considerable quantity of a neutral crystalline solid which, after recrystallisation from alcohol, melted at 183°C. The nitrile was extracted from the mixture by ether, and no further purification was attempted.

The crude nitrile (4 grams) was dissolved in ether and placed over 55 grams potassium bicarbonate dissolved in water; the sodium (12 grams) was then added (method (2)). The distillate gave no picrate. The residue was steam distilled,

and from the ether extract of the distillate 1.8 grams
<u>benzylmethylamine picrate</u> were obtained. On recrystallisation
from alcohol the picrate was deposited as masses of long
yellow needles, m.pt. 117-118°C.

Analysis: Found $C_6H_3O_7N_3 = 66.1\%$

$C_8H_{11}N$, $C_6H_3O_7N_3$ requires $C_6H_3O_7N_3 = 65.4\%$

(I) α-<u>Amino-phenylacetonitrile</u> (Minovici, Ber., 1896, <u>29</u>,
2103) was conveniently prepared from ammonia, benzaldehyde,
potassium cyanide, and acetic acid at 0°C. This procedure
was found to give a much purer product than the method de-
scribed by Minovici who treated mandelonitrile with concen-
trated alcoholic ammonia.

The nitrile was reduced by method (2); 2.5 grams
were reduced with 8.7 grams sodium, 37.5 grams potassium
bicarbonate being employed. The residue gave 2.9 grams
<u>benzylamine picrate</u>, m.pt. and mixed m.pt. 194°C. (Jerusal-
em, J.C.S., 1909, <u>95</u>, 1283.)

(K) α-<u>Methylanilino-phenylacetonitrile</u> (Sachs and Goldmann,
Ber., 1902, <u>35</u>, 3351) was easily obtained by adding acetic
acid to a mixture of benzaldehyde, methylaniline, and pot-
assium cyanide in water.

5 grams nitrile, 10 grams sodium, and 45 grams
potassium bicarbonate were used in the reduction (Method (2)).
The residue was steam distilled, leaving <u>benzyl-methylaniline</u>
which was extracted with ether and isolated as <u>picrate</u>, m.pt.
and mixed m.pt. 104°C. (Komatsu, Mem. Coll. Sci. Kyoto, 1912,
<u>3</u>, 371). The yield of picrate was 4.8 grams.

(L) α-Anilino-α-phenylpropionitrile. Efforts to prepare this nitrile from acetophenone, aniline, potassium cyanide, and acetic acid were unsuccessful; the use of aniline hydrochloride led to no improvement, and eventually the method described by Bucherer and Grolée (Ber., 1906, <u>39</u>, 992) was carried out. Aniline hydrochloride, potassium cyanide, and acetophenone dissolved in petroleum ether were shaken for two hours; the product was washed thoroughly with hot water and then the nitrile was extracted from the residue by ether.
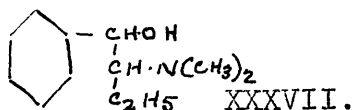
The nitrile was reduced according to method (2), the quantities employed being 5 grams nitrile, 10 grams sodium, and 60 grams potassium bicarbonate. Owing to the low solubility of the nitrile in ether, the reduction had to be carried out in dilute solution, and 2 grams of the nitrile were recovered when petroleum ether was added to the residue; this unchanged material was identified by its m.pt. and mixed m.pt. with the pure compound. The remainder of the product was steam distilled, the residue extracted with ether, and the solvent evaporated off. A solution of the remaining liquid in hot dilute hydrochloric acid deposited <u>α-phenylethyl-aniline hydrochloride</u>, m.pt. 185-186°C. (Busch, Ber., 1904, <u>37</u>, 2691) - 1.73 grams of the hydrochloride were obtained. Analysis: Found HCl = 15.7%

Calculated for $C_{14}H_{15}N, HCl,$ HCl = 15.6%

SUMMARY.

An experiment was performed with benzaldehyde disodium and α-dimethylamino-n-butyronitrile in an attempt to prepare α-hydroxy-α-phenyl-β-dimethylamino -butane (XXXVII); owing to the presence of metallic sodium the nitrile was reduced to dimethyl-n-propylamine.

$$\langle \rangle - \begin{array}{c} \text{CHOH} \\ | \\ \text{CH}\cdot\text{N(CH}_3\text{)}_2 \\ | \\ \text{C}_2\text{H}_5 \end{array} \quad \text{XXXVII.}$$

The apparent ease with which the reduction took place drew attention to the possibility of reducing α-aminonitriles as a method of preparing amines, and some experiments have been carried out for that purpose.

Indications of considerable decomposition of the nitrile were obtained in preliminary experiments with some of the common reducing agents, and the reductions were therefore carried out by other methods. This was done by adding the nitriles in moist ether to atomised sodium (method (1)), and by adding sodium to ethereal solutions of the nitriles floating on strong aqueous potassium bicarbonate (method (2)).

In all the nitriles reduced by method (1) the cyano-group was replaced by hydrogen. This so-called abnormal reaction has also been observed quite frequently in reductions by method (2), but in some cases the CN-group has been reduced to $CH_2.NH_2$.

Taken in conjunction with previous observations, the fact that α-dimethylamino-butyronitrile and α-dimethylamino-

isobutyronitrile each give different types of product when reduced by these two methods would seem to indicate that alkaline conditions favour replacement of the cyano-group by hydrogen in nitriles, whereas acid conditions favour reduction of the cyano-group to $-CH_2.NH_2$.

In reductions by method (2) the presence of a phenyl group in the α-position appears to influence the course of the reaction. All the nitriles possessing such a phenyl group were reduced to monamines i.e. $C \cdot CN \rightarrow C \cdot H$, while those which had no phenyl radical attached to the α-carbon atom were reduced to diamines, i.e. $C-CN \rightarrow C \cdot CH_2NH_2$. These results may be compared with those of the interaction of α-dimethylamino-nitriles and the Grignard reagent; in the latter α-phenylation leads to suppression of the normal reaction of ketone formation in favour of the displacement of the nitrile group by the radical of the Grignard reagent.

Phenylation of the amino-group appears to have no effect on the course of the reduction.

The reduction of α-phenylated α-amino-nitriles by method (2) provides a good general method for the preparation of primary, secondary, and tertiary amines; this method is not suited to the treatment of large quantities.
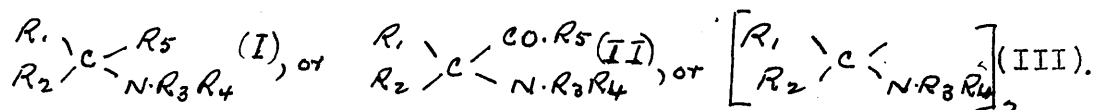

THE INTERACTION OF α-AMINO-NITRILES

AND THE GRIGNARD REAGENT.

DISCUSSION.

As has already been pointed out (p.1), an α-amino-nitrile and a Grignard reagent may react in three ways;[1,2,33] the action of $R_5Mg \cdot x$ upon $R_1 \cdot R_2C(N \cdot R_3R_4)CN$ may result in the formation of

$$\underset{R_2}{\overset{R_1}{\diagdown}}C\underset{N \cdot R_3R_4}{\overset{R_5}{\diagup}} \text{(I)}, \text{ or } \underset{R_2}{\overset{R_1}{\diagdown}}C\underset{N \cdot R_3R_4}{\overset{CO \cdot R_5}{\diagup}} \text{(II)}, \text{ or } \left[\underset{R_2}{\overset{R_1}{\diagdown}}C\underset{N \cdot R_3R_4}{\overset{}{\diagup}}\right]_2 \text{(III)}.$$

Several examples have been recorded in which mixtures of (I) and (II) were produced, but in such cases one of the products was usually obtained in much greater quantity than the other. Reaction (III) has been observed quite frequently by Bruylants and his collaborators who have principally studied piperidino-nitriles.[33]

Thomson and Stevens have made a comprehensive study of the interactions of α-dimethylamino-nitriles and a series of Grignard reagents,[2] and from their results they have drawn the following conclusions:

(a) When $R_1 = R_2 = H$, (II) predominates irrespective of the nature of R_5.

(b) When $R_1 = H$ and R_2 is lower alkyl, (II) predominates if R_5 is alkyl, and (I) if R_5 is the phenyl or benzyl radical.

(c) When $R_1 = H$ and R_2 is the phenyl radical, the main product is always (I).

I.e. the 'normal' Grignard-nitrile reaction of ketone formation always occurs with α-dimethylamino-acetonitrile (rule (a)); the reaction is influenced more strongly in the direction

of double decomposition (I) by phenyl or benzyl magnesium
halides than by alkyl magnesium halides (rule (b)); and
double decomposition (I) is definitely favoured by the inser-
tion of a phenyl group in the α-position to the replaceable
cyano-group of the nitrile. (rule (c)).

In considering their own results along with those
obtained by Bruylants, and by Christiaen,[34] in experiments
with α-piperidino-nitriles, the above authors have commented
upon the sensitiveness of the reaction to small constitutional
changes, and they have pointed out that the replacement of
the dimethylamino- by the piperidino-group in the nitrile re-
sults in the complete suppression of ketone formation (II)
and exclusive formation of (I). They have therefore suggested
that this change in the course of the reaction may be assoc-
iated with the basic strength of the amino-nitrogen atom,
nitriles derived from piperidine undergoing reaction (I) more
readily than those derived from the weaker bases dimethylamine
and ethylaniline.

The experimental evidence upon this point being some-
what scanty, further information was clearly desirable, and
the purpose of the following experiments was to provide the
necessary knowledge.

It is to be noted that this investigation was confined
to an examination of the reactions of tertiary amino-nitriles.
The idea that the basicity of the amino-nitrogen atom is one
of the major factors which control the direction of the reac-
tion is not disposed of by the fact that the interaction of

α-anilino-acetonitrile and methyl magnesium iodide results in double decomposition whereas the interaction of α-ethyl-anilino-acetonitrile and the same Grignard reagent gives ketone formation.[1] Ethylaniline is a stronger base than aniline, but there is a secondary amino-group in the anilino-nitrile, and it is probably the cyano-group of the compound $CN \cdot CH_2 \cdot N$ (Mg. Br.)$\cdot C_6H_5$, and not that of the nitrile, which is replaced.

The reactions of five nitriles, two derived from diethylamine and three from methylaniline, have been studied; the results obtained in the interactions of both α-diethyl-amino-acetonitrile and α-diethylamino-phenylacetonitrile with methyl magnesium iodide and phenyl magnesium bromide, are in support of the above theory, but the type of product produced by α-methylanilino-propionitrile and methyl magnesium iodide makes the suggestion untenable.

For comparison the results obtained with α-diethyl-amino-acetonitrile and those reported by Thomson and Stevens in their study of the reactions of the corresponding dimethyl-amino-nitrile are shown together in Table II. The type of product is indicated by (I) and (II), and the percentage yields are also given.

Table II.

	Me.Mg.I	Ph.Mg.Br.
α-dimethylamino-acetonitrile	(II) 50%[φ]	(II) 78%
α-diethylamino-acetonitrile	(I) 52%	(I) 63%

[φ] A 4% yield of (I) was also obtained.

It would therefore appear that an increase in the basicity of the amino-nitrogen atom favours double decomposition (I).

α-Diethylamino-phenylacetonitrile, like the corresponding dimethylamino-nitrile, gave excellent yields of double decomposition products with the same Grignard reagents.

The investigation of the reaction of α-methylanilino-acetonitrile with methyl magnesium iodide was abandoned owing to the difficulties which were experienced in attempts to identify the product. It was considered that there was no need to prolong the examination in view of the result obtained in the interaction of the same nitrile and phenyl magnesium bromide. In the latter a 59% yield of ketone was produced, and since it has been established that methyl magnesium iodide displays a greater tendency than phenyl magnesium bromide to give ketone formation (rule (b)), it was assumed that the first mentioned reaction had also resulted in ketone formation, and that the product had undergone some rearrangement.

α-Methylanilino-propionitrile and methyl magnesium iodide gave a 73% yield of isopropyl-methylaniline (type I). This result, taken in conjunction with the fact that α-dimethylamino-propionitrile (derived from dimethylamine which is a stronger base than methylaniline) and the same Grignard reagent give a 50% yield of ketone, shows that the basicity of the amino-nitrogen atom cannot be regarded as exerting any great influence on the direction of the reaction.

In the foregoing experiments, and also in those re-

ported by the authorities cited above, the nitrile was
added gradually to the Grignard reagent in anhydrous ether
and the mixture was then allowed to stand at room tempera-
ture for about 15 hours; under these conditions the reactions
proceeded smoothly. After such treatment, however, the
nitrile was recovered unchanged in each of the following ex-
periments: (A)α-methylanilino-propionitrile and phenyl
magnesium bromide; (B) α-methylanilino-phenylacetonitrile
and methyl magnesium iodide; and (C)α-methylanilino-phenyl-
acetonitrile and phenyl magnesium bromide. By heating the
mixture of reactants in boiling toluene for three hours a
good yield of double decomposition product was obtained in
(B), but this modification was not successful in (A) and (C).
In view of the ease with which the others react the non-re-
active character of the methylanilino-nitriles in these
cases was very surprising, particularly since α-methylanilino-
acetonitrile reacts with phenyl magnesium bromide in the
usual manner, as does also α-methylanilino-propionitrile with
methyl magnesium iodide. The experiments in question have
been repeated frequently and there can be no doubt that the
nitriles behave abnormally; in this respect they may be com-
pared with 1-cyano-N-methyl-6: 7-dimethoxy-tetrahydroisoquin-
oline which was also recovered unchanged after treatment with
methyl magnesium iodide .

Experimental.

<u>α-Diethylamino-acetonitrile</u> (Knoevenagel and Mercklin,
Ber., 1904, <u>37</u>, 4089). A poor yield was obtained in an at-
tempt to prepare this nitrile by addition of acetic acid to
a mixture of diethylamine, potassium cyanide, and formalin.
The method employed by the authors quoted gave excellent
yields; aqueous potassium cyanide was added to a mixture of
diethylamine and the formaldehyde bisulphite compound in
water.

(1) Treatment with methyl magnesium iodide.

The Grignard reagent was prepared in anhydrous ether
from 3.2 grams magnesium and 18 grams methyl iodide, and
cooled in a mixture of ice and salt. An ethereal solution
of the nitrile (5.7 grams) was then added slowly, and the
mixture was allowed to stand for about 15 hours. At the end
of this period crushed ice was added, care being taken to
avoid loss of any volatile material, and when the reaction
had subsided, a mixture of 25 grams concentrated sulphuric
acid and 25 c.c.s. water was introduced. The acid layer was
separated, transferred to a distillation apparatus, and made
alkaline by addition of a strong aqueous solution of 35 grams
potassium hydroxide. The reaction mixture was then steam
distilled into dilute hydrochloric acid, the distillation
being stopped when the distillate was no longer alkaline.
The acid solution was evaporated to dryness on the water bath.

The residue was covered with ether and basified by addition of strong sodium hydroxide solution; the ether layer was separated and dried over potassium carbonate. The solvent was then distilled off on the boiling water bath, and from the distillate triethylamine was isolated as picrate (8.7 grams); only a very small quantity of dark coloured residue was left, and from it further traces of the same product were obtained. No other basic product was isolated. After recrystallisation from alcohol the above picrate melted at 173°C. (Jerusalem, J.C.S., 1909, **95**, 1281); the yield was 52% of the theoretical.

Analysis: Found $C_6H_3O_4N_3 = 69.8\%$

   Calc. for $C_6H_{15}N, C_6H_3O_4N_3 ; C_6H_3O_4N_3 = 69.4\%$

Any diethylamino-acetone (boiling point 155-156°C.) formed in the reaction would have been found in the residue after removal of the ether, and would therefore have been easily detected. There was no indication of its presence.

   As an alternative to steam distillation, the following procedure was adopted in a repetition of the above experiment. The reaction mixture of Grignard reagent and nitrile was treated with ice as before; hydrochloric acid was then added and the acid layer was separated and evaporated to dryness on the water bath. The residue, which consisted largely of magnesium chloride, was then covered with ether and basified; the subsequent treatment was the same as before. On this occasion the yield of triethylamine, again isolated as picrate, was only

about 30%. No other product was obtained.

(2) Treatment with phenyl magnesium bromide.

Upon this occasion the "standard" conditions were employed. Phenyl magnesium bromide was prepared in anhydrous ether from 10.8 grams magnesium and 44.5 c.c.s. bromobenzene. The Grignard reagent was cooled in ice and salt and to it the nitrile (18 grams), dissolved in ether, was added gradually. After standing at room temperature for about 15 hours, a mixture of ice and ammonium chloride was added; the ether layer was separated and dried over potassium carbonate.

After evaporation of the solvent the product was fractionated under reduced pressure, 13.5 grams benzyl-diethylamine, boiling at 100-105°under 12 m.m. pressure, were obtained along with 6 grams of a higher boiling fraction. On examination, the second fraction was found to consist of a mixture of the same base (3 grams) and di-phenyl, melting point and mixed melting point 71°C. The picrate of the base was prepared; after recrystallisation from alcohol it melted at 120°C. (Flürscheim and Holmes, J.C.S., 1926, 127, 1568). Yield 63%.

Analysis:

Found $C_6H_3O_4N_3 = 58.4\%$

Calc. for $C_{11}H_{14}N, C_6H_3O_4N_3$; $C_6H_3O_4N_3 = 58.4\%$

α-Diethylamino-phenylacetonitrile (Knoevenagel and Mercklin, Ber., 1904, __37__, 4090) was prepared in fairly good yield from benzaldehyde, diethylamine, potassium cyanide, and acetic acid in water.

(1) Treatment with methyl magnesium iodide.

The experiment was conducted under the "standard" conditions described above with the following quantities: 5.9 grams nitrile, 2 grams magnesium, and 9.5 grams methyl magnesium iodide. No attempt was made to distil the product, α-phenylethyl-diethylamine; it was converted directly to the picrate, which, after recrystallisation from alcohol, melted at 132-133°C.

Analysis:

$$\text{Found} \quad C_6H_3O_4N_3 = 56.6\%$$

$C_{12}H_{19}N, C_6H_3O_4N_3$ requires $C_6H_3O_4N_3 = 56.4\%$

The yield of picrate was 12 grams. % yield = 94%

(2) Treatment with phenyl magnesium bromide.

The experiment was conducted as in (1) with 5.9 grams nitrile and the Grignard reagent prepared from 2 grams magnesium and 10.4 grams bromobenzene. As before the product, benzhydryl-diethylamine, was converted directly to the picrate. The yield of picrate was 13.5 grams; after recrystallisation from alcohol it melted at 183°C.

Analysis:

$$\text{Found} \quad C_6H_3O_4N_3 = 48.9\%$$

$$C_{14}H_{21}N, C_6H_3O_4N_3 \quad \text{requires} \quad C_6H_3O_4N_3 = 48.9\%$$

A specimen of <u>benzhydryl-diethylamine hydrochloride</u> was also prepared; it was recrystallised from alcohol and melted at 172-173°C.

Analysis:

$$\text{Found} \quad HCl = 13.2\%$$

$$C_{14}H_{21}N, HCl \quad \text{requires} \quad HCl = 13.2\%$$

In the above experiment the yield of benzhydryl-diethylamine was equivalent to 92% of the theoretical.

<u>α-Diethylamino-propionitrile</u> (Knoevenagel and Mercklin, Ber., 1904, <u>37</u>, 4089). An unsuccessful attempt was made to prepare the nitrile from a mixture of diethylamine, acetaldehyde, potassium cyanide, and acetic acid in water; this method is not of much value with proprionitriles in general owing to the readiness with which acetaldehyde resinifies on coming into contact with potassium cyanide. Knoevenagel and Mercklin claim that this nitrile can be prepared in good yield by adding aqueous potassium cyanide to a mixture of diethylamine and acetaldehyde sodium bisulphite in water; this procedure was tried out unsuccessfully on two occasions. In view of the other results, an examination of the reactions of this

nitrile was not considered to be essential, and no further effort was made to obtain the substance. It is of interest to note, however, that Stewart and Korpi (J.Am.C.S., 1932, 54, 3987) have stated that α-diethylamino-propionitrile is best prepared from acetaldehyde cyanhydrin and diethylamine. This method, which is much more troublesome than the bisulphite method, was also employed by Klages (J. pr. Chem., 1902, 65, 196) and a modification of it was used by Cocker, Lapworth, and Walton (J.C.S., 1930, 440).

α-Methylanilino-acetonitrile. (Warunis and Sachs, Ber., 1904, 37, 2636). The addition of acetic acid to a mixture of methylaniline, formalin, and potassium cyanide in water gave a very poor yield of nitrile; all the usual modifications of this method gave equally poor results. It was therefore necessary to prepare the compound from formaldehyde cyanhydrin and methyl-aniline as directed by Warunis and Sachs. Anhydrous hydrocyanic acid was obtained by dropping 50% sulphuric acid upon potassium cyanide (Wade and Panting, J.C.S., 1898, 73, 255); on adding a drop of aqueous potassium cyanide to a mixture of the product and formalin a violent reaction took place, formaldehyde cyanhydrin being produced in excellent yield (Ultée, Rec. d. Trav. Chim. d. Pays-Bas, 1909, 28, 248). The cyanhydrin was heated with methylaniline in a sealed tube for three hours at 120-125°C.

(1) Treatment with methyl magnesium iodide.

The nitrile (6.2 grams) was treated with methyl magnesium iodide, prepared from 3 grams magnesium and 15 grams methyl iodide, and the product was worked up according to the standard procedure. On fractionation under reduced pressure 4 grams of a reddish liquid, boiling at 140-150°C. under 12 m.m. pressure, were obtained. On addition of ethereal picric acid to a sample of this material, a deep red colouration was developed but no picrate was deposited. Similar treatment with p-bromphenacyl bromide also gave a negative result.

This substance could not have been the double decomposition product, methylethylaniline, since the latter boils at 201°C. under ordinary pressure (Claus and Howitz, Ber., 1884, 17, 1325), and its failure to produce an insoluble yellow picrate showed that it was not N-acetonyl-methylaniline (Meisenheimer, Angermann, Finn, and Vieweg, Ber., 1924, 57, 1744).

It is possible that N-acetonyl-methylaniline was produced in the reaction and was then converted to 1:3-dimethylindole by loss of water. The latter boils at 120°C. under 7 m.m. pressure and forms a red picrate soluble in ether (M., A., F., and V., loc. cit.), but no definite evidence upon this point is available. For the reasons given previously the examination was not continued.

(2) Treatment with phenyl magnesium bromide.

The experiment was carried out as before with 3 grams nitrile, 1.5 grams magnesium, and 8 grams bromobenzene. On evaporation of the ether, 2.7 grams of a slightly yellowish solid were obtained; after recrystallisation from alcohol the product melted at 120°C. Its mixed melting point showed that it was identical with a specimen of ω-methylanilino-acetophenone prepared by heating methylaniline (2 mols.) with phenacyl bromide (1 mol.) in benzene solution on the water bath. (Staedel and Siepermann, Ber., 1880, 13, 843). Yield 58.5%.

α-Methylanilino-proprionitrile (Sachs and Kraft, Ber., 1903, 36, 758). The nitrile could not be prepared by addition of acetic acid to a mixture of methylaniline, acetaldehyde, and potassium cyanide in water; other modifications of the same method were also unsuccessful. It was prepared in poor yield by the following process.

25 grams sodium bisulphite were dissolved in water (70 c.c.s.) and to the solution 11.5 grams acetaldehyde were added. This was followed by addition of 25 grams methylaniline and the mixture was heated on the boiling water bath. There was no apparent solution of the methylaniline. An aqueous solution of 16.5 grams potassium cyanide was then added and the whole was heated for about an hour. On cooling the mixture was extracted with ether; after evaporation of the solvent the product was fractionated under reduced

pressure. 8 grams of the nitrile and a considerable quantity of unchanged methylaniline were obtained.

The nitrile was also prepared from methylaniline and acetaldehyde cyanhydrin (Ultée, loc. cit.) in the same way as α-methylanilino-acetonitrile. Instead of heating the mixture in a sealed tube, it was found that the nitrile could be prepared equally well by heating methylaniline and the cyanhydrin in the presence of excess lime in an open vessel on the oil bath at 120°C.

(1) Treatment with methyl magnesium iodide.

6.6 grams nitrile, 3 grams magnesium, and 15 grams methyl iodide were employed in an experiment performed according to the standard procedure; the product was distilled under reduced pressure. Isopropyl-methylaniline (4.5 grams) was obtained as an almost colourless liquid boiling at 100-105°C. under 12 m.m. pressure. From it and benzyl iodide, phenyl-benzyl-methyl-isopropyl ammonium iodide was prepared; after recrystallisation from methylated spirit this substance melted at 133°C. (Thomas and Jones, J.C.S., 1906, 89, 287).

The picrate was prepared in ether; it was recrystallised from alcohol, melting point 112-113°C.

Analysis:

$$\text{Found} \qquad C_6H_3O_4N_3 = 60.9\%$$

$$C_{10}H_{15}N, C_6H_3O_4N_3 \text{ requires } C_6H_3O_4N_3 = 60.6\%$$

The yield of isopropyl-methyl-aniline was 73% of the theoretical; no other product could be isolated.

(2) Treatment with phenyl magnesium bromide.

An experiment was carried out in the usual manner with 8.1 grams nitrile and the Grignard reagent prepared from 2.8 grams magnesium and 16 grams bromobenzene. On fractionation of the product under reduced pressure 7.5 grams of the nitrile were recovered. The experiment was repeated and again the nitrile was recovered.

The method was therefore modified as follows. Phenyl magnesium bromide was prepared in anhydrous ether, 2.4 grams of magnesium and 10 c.c.s. bromobenzene being employed; pure dry toluene was then added and the excess ether was distilled off. The nitrile (6 grams) was dissolved in toluene and added to the Grignard reagent, and the mixture was heated under reflux for three hours. After cooling, a mixture of ice and ammonium chloride was added and the toluene layer was separated and dried over potassium carbonate. The toluene was distilled off; on passing anhydrous hygrogen chloride through the distillate methylaniline hydrochloride was obtained, melting point and mixed melting point with an authentic specimen 121-122°C. (Menschutken, Jour. d. Russ-Phys. Chem. Gesell., 1898, 30, 252). The residue remaining after removal of the toluene distilled up to 190°C. under reduced pressure, but no definite fractions were obtained. Dry hydrogen chloride was passed through an ethereal solution of this material and a white solid (X) was deposited immediately; this substance was filtered off, and from the ether a few well developed crystals

(Y) separated on standing. The substances X and Y were not
identical. After recrystallisation from alcohol X was found
to melt and decompose at about 190°C; it turned red on melting
and the melting point varied according to the rate of heating.
It contained 19.5% of hydrogen chloride. It was very probably
the hydrochloride of the original nitrile. For purposes of
comparison the hydrochloride of the nitrile was prepared; it
displayed the same characteristics as X, but the percentage
of hydrogen chloride was somewhat higher. The calculated
percentage is 18.6, but in view of the instability of α-amino-
nitriles it is not surprising that the observed figures are
high. It would be very difficult, if not impossible, to obtain
α-methylanilino-propionitrile hydrochloride free from methyl-
aniline hydrochloride.

By its m.pt. and mixed m.pt. Y was found to be iden-
tical with the hydrochloride of α-phenylethyl-methylaniline
which was prepared from α-methylanilino-phenylacetonitrile and
methyl magnesium iodide (see below).

α-Methylanilino-phenylacetonitrile (Sachs and Goldmann, Ber.,
1902, 35, 3352) was easily prepared by addition of acetic acid
to a mixture of methylaniline, benzaldehyde, and potassium
cyanide in water. It was recrystallised from alcohol.

(1) Treatment with methyl magnesium iodide.
A preliminary experiment gave unsatisfactory results, and on
repeating the experiment on a larger scale most of the nitrile
was recovered. A modified experiment was more successful.

Methyl magnesium iodide was prepared in ether from
3.2 grams magnesium and 7.7 c.c.s methyl iodide. Pure dry
toluene was added and the excess ether was distilled off. The
nitrile (8 grams) in toluene, was then added and the mixture
was boiled for three hours; on cooling,ice and ammonium chlor-
ide were added and the toluene was separated and dried over potas-
sium carbonate. The toluene was removed by distillation. On
fractionation of the residue 5.8 grams α-phenylethylmethyl-
aniline, b.pt. 178°C. under 15 m.m. pressure, were obtained.
This yield was 76%, of the theoretical.

A specimen was converted to the hydrochloride. After
recrystallisation from alcohol it melted at 167-8°C.

Analysis: Found HCl = 14.5%

$C_{15}H_{17}N,HCl$ requires HCl = 14.7%

The picrate was prepared and recrystallised from alcohol; it
was deposited as a deep yellow, crystalline solid, m.pt. 132°C.

Analysis: Found $C_6H_3O_7N_3$ = 51.9%

$C_{15}H_{17}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$ = 52.5%

(2) Treatment with phenyl magnesium bromide.

As in (1) the nitrile was recovered unchanged in ex-
periments conducted under the 'standard' conditions. The mod-
ification previously described was therefore employed in an
experiment with 6.45 grams nitrile, 2 grams magnesium, and
7.7 c.c.s bromobenzene. From the toluene distillate methyl-
aniline hydrochloride was isolated in small traces and identif-
ied by its melting point and mixed melting point.

From the residue left after removal of the toluene
two substances were isolated in small quantity. The first
of these boiled at 200°C. under reduced pressure and was
found to be unchanged nitrile (m.pt. and mixed m.pt. 67°C.).
The second boiled at 280°C. under 15 m.m. pressure and con-
densed to a gum which separated from methyl alcohol as a yellow
crystalline solid, m.pt. 170-172°C. All efforts to identify
this substance were unsuccessful.

SUMMARY.

From the results obtained in previous investigations of the interaction of α-amino-nitriles and the Grignard reagent it has been suggested that a nitrile derived from a strong base will undergo double decomposition more readily than one derived from a weak base. This theory has now been disproved. α-Methylanilino-propionitrile and methyl magnesium iodide have been shown to give isopropyl-methyl-aniline, a double decomposition product, and it was previously known that α-dimethylamino-propionitrile, which is derived from a stronger base, and the same Grignard reagent undergo ketone formation.

α-Methylanilino-phenylacetonitrile and α-methylanilino-propionitrile are remarkably non-reactive towards phenyl magnesium bromide, and it is only under special conditions that the first of these reacts with methyl magnesium iodide.

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