[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

CONDENSATIONS OF NITRILES HAVING α-HYDROGEN TO FORM β-IMINONITRILES, CYCLIC TRIMERS, AND SUBSTITUTED 2-HYDROXY-4-AMINOPYRIDINES[1]

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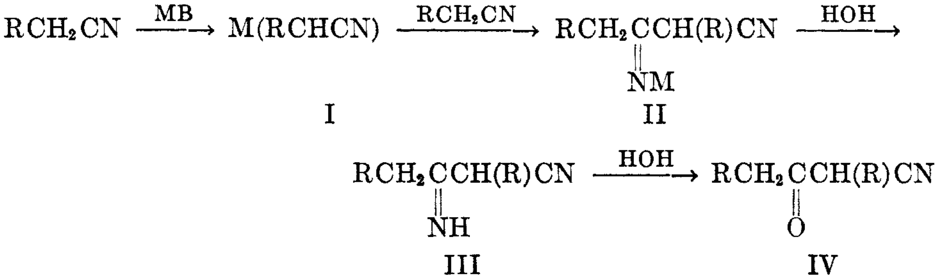
The α-hydrogen of nitriles may be removed by appropriate metallic basic reagents (MB or Na) to form the nitrile anion or metallic derivative (I) which may condense with unchanged nitrile to form the metallic derivative of the β-iminonitrile (II). Careful hydrolysis of II yields the β-iminonitrile (III), the dimer, which on further hydrolysis forms the β-ketonitrile (IV).



$$RCH_2CN \xrightarrow{MB} \underset{I}{M(RCHCN)} \xrightarrow{RCH_2CN} \underset{II}{RCH_2\underset{\underset{NM}{\|}}{C}CH(R)CN} \xrightarrow{HOH}$$

$$\underset{III}{RCH_2\underset{\underset{NH}{\|}}{C}CH(R)CN} \xrightarrow{HOH} \underset{IV}{RCH_2\underset{\underset{O}{\|}}{C}CH(R)CN}$$

Under more drastic conditions, there may be formed cyclic trimers of the pyrimidine and pyridine types, V and VI, respectively. Trimer V may be accounted for by the nitrogen-carbon condensation of II with the nitrile group of unchanged nitrile followed by cyclization, and trimer VI, by the carbon-carbon condensation of I with the nitrile group of II followed by cyclization.

Of course basic reagents may react with the nitrile group instead of with the α-hydrogen of nitriles. For example, Grignard reagents may add to the nitrile group to form ketimines or ketones and sodium amide may add to form amidines. Although this course of reaction often predominates, reaction at the α-hydrogen to produce dimers and trimers has been realized satisfactorily with certain nitriles, especially with phenylacetonitrile which has a relatively reactive α-hydrogen.

Earlier workers have reported the formation of dimers[2] or trimers from certain nitriles by Grignard reagents (1), sodium alkoxides (2), sodium (2d, 3), and sodium amide (2d). However, except in a few cases, the yields were unsatisfactory or not reported, or the methods were rather inconvenient.

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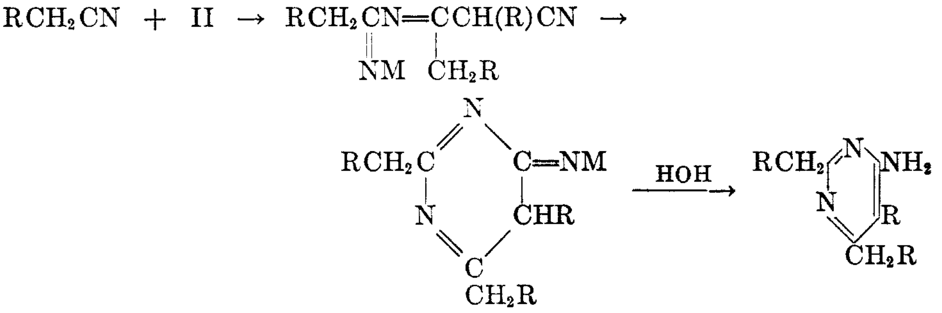
[2] β-Ketonitriles (IV), obtained on hydrolysis of the dimer (III), have been prepared by various workers, notably Ziegler who generally employed lithium dialkylamines. See Ziegler, Eberle, and Ohlinger, *Ann.*, **504**, 94 (1933).

We have developed convenient methods for the preparation of dimers and trimers in satisfactory yield from typical nitriles by means of certain basic reagents. In general, the same basic reagent produced mainly the dimer in refluxing ethyl ether or other relatively low-boiling solvent and mainly the trimer in refluxing *n*-butyl ether. Diisopropylaminomagnesium bromide, which is abreviated to DIPAM, was chosen as one of the reagents because it has previously been found to effect in satisfactory yield analogous α-hydrogen reactions with various esters to form the corresponding β-ketoesters (4).



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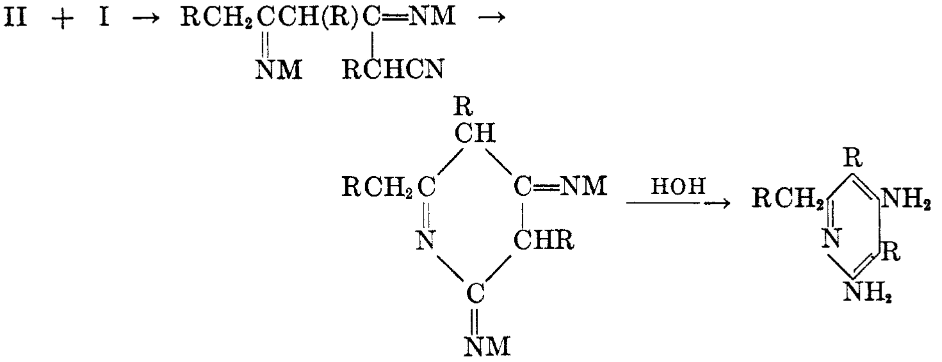


VI

It can be seen from Table I that satisfactory yields (50–80%) of the dimers were obtained in refluxing ethyl ether from acetonitrile with sodium, from propionitrile with DIPAM or sodium, from valeronitrile with DIPAM, and from phenylacetonitrile with DIPAM, sodium amide, or sodium hydride. With the last reagent, the dimer α,γ-diphenyl-β-iminobutyronitrile was isolated as the β-ketonitrile. Our result from acetonitrile with sodium confirms that reported by Holtzwart (3a). The dimer from phenylacetonitrile has been reported in 70% yield with refluxing alcoholic sodium ethoxide under controlled conditions (2a) and in yields up to 80% with certain Grignard reagents (1a).

Satisfactory yields (50–90%) of the pyrimidine trimer (V) were obtained in refluxing *n*-butyl ether from acetonitrile with sodium, from propionitrile with DIPAM, and from phenylacetonitrile with sodium amide. The theoretical ratio of three moles of nitrile to one mole of the basic reagent was employed in these reactions (see above equations). Earlier workers have reported satisfactory yields of the pyrimidine trimer from acetonitrile with sodium (3g) or sodium methoxide (2e), from propionitrile with sodium (3i) or lithium (2d), and from phenylacetonitrile with sodium ethoxide (2c); however, in each of these cases, sealed tubes or other pressure devices were employed. A good yield of the trimer from phenylacetonitrile has also been reported with sodium amide (2d) but the procedure has not been available.

When the theoretical ratio of three moles of phenylacetonitrile to two moles of DIPAM was employed in refluxing *n*-butyl ether or, better, when equivalent amounts of the reactants were used in this solvent, the pyridine trimer (VI) was produced. Earlier workers have obtained this trimer in yields of 10–35% by means of certain Grignard reagents (1b, c). We made unsuccessful attempts to prepare the pyridine trimers from acetonitrile and propionitrile.

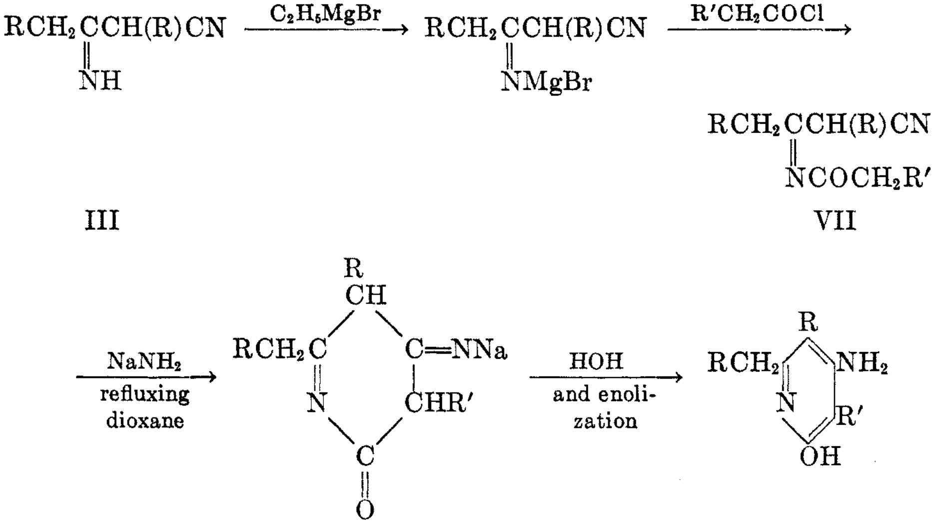
TABLE I

RESULTS WITH NITRILES AND BASIC REAGENTS IN REFLUXING ETHYL ETHER (DIMER FORMATION)

NITRILE	BASIC REAGENT	DIMER	M.P., °C.	B.P., °C.	MM.	YIELD, %
Aceto-	DIPAM[a]	III, R = H	52–53[b]	108	3	5[c]
Aceto-	Sodium	III, R = H	52–53[b]	108	3	70
Propio-	DIPAM[a]	III, R = CH_3	47–48[d]	150–151	20	65
Propio-	Sodium	III, R = CH_3	47–48[d]	150–151	20	50
Propio-	Sodium hydride[e]	IV, R = CH_3[f]		190–194[g]		20[h]
Valero-	DIPAM[a]	III, R = C_4H_9		170–173[i]	10	50
Valero-	Sodium	III, R = C_4H_9		170–173[i]	10	25
Phenylaceto-	DIPAM[a]	III, R = C_6H_5		238–240[j]	5	80
Phenylaceto-	Sodium amide	III, R = C_6H_5		238–240[j]	5	79
Phenylaceto-	Sodium hydride[e]	IV, R = C_6H_5[f]	85–86[k]	197–205	3	78
Phenylaceto-	Sodium	III, R = C_6H_5		238–240[j]	5	35[l]

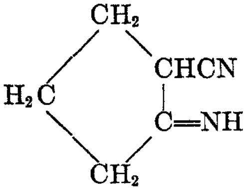
[a] Diisopropylaminomagnesium bromide. [b] See ref. 3b. [c] A 35% yield of the trimer (V, R = H) was also obtained along with considerable recovered nitrile. [d] See ref. 3d. [e] Benzene was used as the solvent. [f] The dimer was isolated as the β-ketonitrile. [g] See ref. 1d. [h] A considerable amount of unidentified solid was also obtained. [i] *Anal.* Calc'd for $C_{10}H_{18}N_2$: N, 16.85. Found: N, 17.00. [j] Atkinson and Thorpe (ref. 2a) reported b.p. 274° at 20 mm. The compound was further identified by hydrolysis to the β-ketonitrile, m.p. 85–86° in agreement with reported value (see note k). [k] Walther and Schickler, *J. prakt. Chem.*, [2] 55, 351 (1897). [l] A 35% yield of the trimer (V, R = C_6H_5) was also obtained.

The β-iminonitriles (III) from the self-condensation of acetonitrile, propionitrile, and phenylacetonitrile were converted to their magnesium derivatives by ethylmagnesium bromide, and the magnesium derivatives acylated with certain acid chlorides or anhydrides. The yields of the resulting acyl derivatives (VII) were quite satisfactory (Table II). The magnesium derivatives produced in the reaction mixtures from the self-condensation of phenylacetonitrile and propionitrile by DIPAM were also acetylated (without first isolating the β-iminonitrile), but the yields were lower. The acyl derivatives were cyclized by sodium amide in refluxing dioxane to form 2-hydroxy-4-aminopyridines (VIII). All but one of the acyl derivatives studied gave satisfactory yields of cyclic products (Table III). The acyl derivative in which both R and R′ are hydrogen appeared to cyclize, but the product was not obtained pure enough for analysis.



III VII VIII

Schroeder and Rigby (5) have acylated with anhydrides the free cyclic β-iminonitrile (IX) which was prepared by the intramolecular self-condensation of adiponitrile. They cyclized the resulting acyl derivatives (X) with sodium amide in liquid ammonia or in mineral oil at 200° to form 4-amino-6,7-dihydro-1,5*H*-pyrindin-2-ol (XI). However, we were unsuccessful in attempts to acylate free β-iminonitriles of type III (R = C_6H_5 and CH_3), and in attempts to cyclize acyl derivatives of type VII (R = C_6H_5 and CH_3) with sodium amide in liquid ammonia. Their other method of cyclization employing sodium amide in hot mineral oil might be satisfactory with acyl derivatives of type VII since we found the cyclization to proceed satisfactorily at the temperature of refluxing dioxane.



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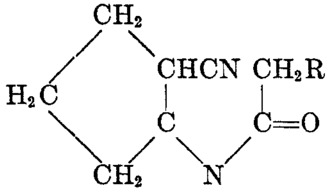

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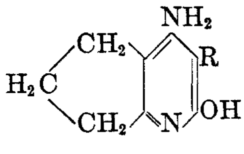

XI

EXPERIMENTAL[3]

Apparatus. The apparatus employed consisted of a three-necked, round-bottomed flask of suitable capacity equipped with a dropping-funnel, mercury-sealed stirrer, and a reflux condenser capped with a tube containing Drierite. In reactions with sodium hydride, a wet-test meter connected to the outlet end of the condenser was used to measure the evolved hydrogen (6).

Self-condensations of nitriles by basic reagents in ethyl ether and other low-boiling solvents. The procedures for the condensations by the various basic reagents are described below. The ether solutions of the β-iminonitriles or other products were dried over Drierite, the solvent removed, and the residue fractionated *in vacuo* through a 15-cm. Vigreux column. The results are summarized in Table I.

(A) *With diisopropylaminomagnesium bromide.* Preliminary experiments with phenylacetonitrile indicated that, although the conversion yield to dimer was better with a two to one ratio of nitrile to basic reagent, the actual yield was better with equivalent amounts of nitrile and basic reagent. Doubling the reaction time or the use of a slight excess of basic reagent lowered the yield. The experiments listed in Table I were carried out by the following procedure using equivalent amounts of reactants.

To a stirred suspension of 0.5 mole of the reagent (4) in 300 ml. of ethyl ether in a 500-ml. flask was added 0.5 mole of the nitrile in an equal volume of anhydrous ethyl ether at such a rate that gentle refluxing was maintained. A heavy green gum formed. The mixture was refluxed for four hours on the steam-bath, then cooled in an ice-bath and decomposed by the addition of slightly more than the calculated amount of ammonium chloride (30 g.) in 100 ml. of water. After separating the two phases, the aqueous phase was extracted twice with ether and the ether extracts added to the original ether phase. The products were isolated from the combined ether solution.

The β-iminonitriles from phenylacetonitrile and propionitrile (see Table I) were hydrolyzed by dilute hydrochloric acid to form the corresponding β-ketonitriles practically quantitatively.

(B) *With metallic sodium.* To a solution of one mole of the nitrile in an equal volume of ethyl ether or petroleum ether (b.p. 30–60°) was added 0.435 mole of sodium in small pieces at such a rate that gentle refluxing was maintained. After the reaction had subsided, the mixture was refluxed and stirred on the steam-bath for four hours. The solid was washed with a little ether and carefully dissolved in the minimum quantity of water (in case any unreacted sodium was present). The aqueous mixture was thoroughly extracted with ether and the products isolated from the combined ether extracts.

(C) *With sodium amide.* To a suspension of 0.09 mole of sodium amide in liquid ammonia (7) was added 0.09 mole of the nitrile and the mixture stirred for 15 minutes. Then an equal amount of the nitrile in 50 ml. of anhydrous ethyl ether was slowly added. The ammonia was replaced by ether and the mixture stirred and refluxed for 1½ hours. Water was added and the products were isolated from the ether phase which had been combined with several ether extracts of the aqueous phase.

(D) *With sodium hydride.* Sodium hydride (9.6 g., 0.4 mole) was charged to a 1-l. flask which had previously been purged with nitrogen (6). The dry powder was covered immediately with 50 ml. of dry benzene. The nitrile (0.4 mole) was added dropwise during about 30 minutes while the reaction mixture was stirred and heated slowly to 80°, where the evolution of hydrogen began. Stirring and gentle refluxing were continued for two hours about 200 ml. of benzene being added during this time to keep the mixture fluid. After cooling, 300 ml. of ether was added and 20 ml. of absolute ethanol was dropped in slowly to decompose any remaining sodium hydride. The reaction mixture was poured onto 300 g.

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[3] Boiling points are uncorrected; melting points are corrected. Microanalysis are by Clark Microanalytical Laboratory, Urbana, Illinois.

of ice and acidified with a slight excess of concentrated hydrochloric acid. The organic phase was washed with sodium bicarbonate solution and dried. After removal of the solvents, the residue was refluxed gently for 30 minutes with a mixture of 10 ml. of concentrated hydrochloric acid in 200 ml. of water in order to hydrolyze the β-iminonitrile to the β-ketonitrile. The organic phase was again taken up in ether. The ether solution was washed with sodium bicarbonate solution.

Self-condensations of nitriles by basic reagents in n-butyl ether. These reactions were carried out essentially as described above for the reactions in ethyl ether.

(A) *With diisopropylaminomagnesium bromide.* This reagent was prepared either directly in *n*-butyl ether or first in ethyl ether (4) which was then distilled off as an equal volume of *n*-butyl ether was added.

To 0.1 mole of the reagent in 75 ml. of butyl ether was added 0.3 mole of propionitrile in an equal volume of *n*-butyl ether and the mixture was refluxed for four hours. After cooling to room temperature, the butyl ether was decanted and the solid residue treated with a mixture of the calculated amount of hydrochloric acid in 100 ml. of ethanol. The resulting mixture was heated to boiling, suction-filtered, and concentrated under reduced pressure until most of the alcohol was removed. The residue was recrystallized from water, yielding 10.5 g. (66%) of the pyrimidine trimer (V, R = CH_3), m.p. 188–189° [reported m.p. 188–189° (3i)].

To 0.3 mole of the reagent in 100 ml. of butyl ether was added 0.3 mole of phenylacetonitrile in an equal volume of butyl ether and the mixture was refluxed for three hours. On working up the mixture as described above there was obtained, after recrystallization from benzene, 8.7 g. (25%) of the pyridine trimer (VI, R = C_6H_5) m.p. 176–178° [reported m.p. 178–179° (1c)]. The pyridine trimer was also obtained using 0.3 mole of the nitrile and 0.2 mole of the reagent, but the yield was much lower. With 0.3 mole each of propionitrile and the reagent under similar conditions, there was obtained, after recrystallization from a mixture of benzene and ligroin (b.p. 90–120°), 10.2 g. of an unidentified compound melting at 244–245° which failed to analyze for a trimer.

(B) *With sodium.* To 0.5 mole of acetonitrile in 100 ml. of butyl ether was added 0.167 mole of sodium and the mixture was refluxed for four hours. The solid was added carefully to 100 ml. of water. The aqueous mixture was suction-filtered and the solid recrystallized from a mixture of benzene and ligroin (b.p. 90–120°) yielding 9.8 g. (48%) of the trimer (V, R = H), m.p. 180–181° [reported m.p. 180–181° (3g)].

An attempt was made to prepare the pyridine trimer from acetonitrile employing 0.5 mole each of the reactants; however, the pyrimidine trimer (25%) was again obtained together with the dimer (29%).

(C) *With sodium amide.* To 0.09 mole of sodium amide in liquid ammonia was added 0.09 mole of phenylacetonitrile and the mixture was stirred for 15 minutes. Then, an additional 0.18 mole of phenylacetonitrile in 50 ml. of butyl ether was added and the liquid ammonia was evaporated while adding 50 ml. more of butyl ether. After refluxing for three hours, the reaction mixture was cooled and water added. The solid was collected. More solid was obtained by removing the solvent from the butyl ether phase of the filtrate. The combined solid was recrystallized from ligroin (b.p. 90–120°) yielding 28 g. (89%) of the pyrimidine trimer (V, R = C_6H_5) m.p. 106–107° [reported m.p. 106–107° (2a)].

An attempt was made to prepare the pyridine trimer by using 0.27 mole of phenylacetonitrile and 0.2 mole of sodium amide but the pyrimidine trimer was obtained in low yield (5%).

Mixed nitrile condensation. To a suspension of sodium amide (0.2 mole) in 150 ml. of liquid ammonia was added 23.4 g. (0.2 mole) of phenylacetonitrile in an equal volume of dry ethyl ether. The mixture was stirred for 15 minutes and benzonitrile in 50 ml. of ethyether was slowly added. The ammonia was replaced by 100 ml. of ethyl ether and the mixture was refluxed on the steam-bath for three hours. Water was added and the light pink solid was recrystallized from a mixture of ethanol and water to yield 26 g. (60%) of α,β-diphenyll β-iminopropionitrile, m.p. 145–146°; reported m.p. 145–146° (8). Hydrolysis with dilute acid yielded 23 g. (85%) of β-benzoylphenylacetonitrile b.p. 88–90°; [reported b.p. 89–90° (9)].

TABLE II

ACYLATIONS OF BROMOMAGNESIUM DERIVATIVES OF β-IMINONITRILES TO FORM ACYL DERIVATIVES (VII)

β-IMINONITRILE (III)	ACID CHLORIDE	ACYL DERIVATIVE (VII)	M.P., °C.	YIELD, %	ANALYSIS					
					Calc'd			Found		
					C	H	N	C	H	N
R = H	Acetyl	R = H, R′ = H	128–130[a]	62			22.51			22.40
R = CH_3	Acetyl[b]	R = CH_3, R′ = H	B.p. 165–166 at 3 mm.	65			18.41			18.58
R = CH_3	Phenylacetyl	R = CH_3, R′ = C_6H_5	122–123[c]	60	73.59	7.06	12.26	73.31	7.13	12.21
R = C_6H_5	Acetyl[d]	R = C_6H_5, R′ = H	169–170[c]	65	78.24	5.83	10.14	78.57	5.94	10.25
R = C_6H_5	Propionyl	R = C_6H_5, R′ = CH_3	152–153[e]	75	78.61	6.24	9.64	78.80	5.96	9.76

[a] Recrystallized from ligroin (b.p. 90–120°). [b] The yield was 40–50% with acetic anhydride. In certain runs with this reagent there was obtained a solid melting at 170° which gave essentially the same analytical values. It seems possible that this was another isomeric form of the acyl derivative. [c] Recrystallized from a mixture of benzene and ligroin (b.p. 90–120°). [d] The yield was also 65% with acetic anhydride. Recrystallized from ligroin (b.p. 60–90°).

TABLE III

CYCLIZATION OF ACYL DERIVATIVES (VII) TO FORM 2-HYDROXY-4-AMINOPYRIDINES (VIII)

ACYL DERIVATIVES (VII)	CYCLIC PRODUCT (VIII)	M.P., °C.	YIELD, %	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
R = CH_3, R′ = H	R = CH_3, R′ = H	288	73[a]	63.13	7.92	18.38	62.85	7.87	18.36
R = CH_3, R′ = C_6H_5	R = CH_3, R′ = C_6H_5	224–225	90[b]			12.26			11.99
R = C_6H_5, R′ = H	R = C_6H_5, R′ = H	245–246	86[c]	78.24	5.83	10.14	78.03	5.80	10.04
R = C_6H_5, R′ = CH_3	R = C_6H_5, R′ = CH_3	214–215	82[c]			9.64			9.81

[a] Recrystallized from water. [b] Recrystallized from a mixture of benzene and ligroin (b.p. 90–120°). [c] Recrystallized from a mixture of ethanol and water.

Acylations of β-iminonitriles. To 0.1 mole of ethylmagnesium bromide in 100 ml. of ethyl ether was added 0.1 mole of the β-iminonitrile in 50 ml. of dry benzene. The ether was replaced by 100 ml. of benzene and 0.55 mole of the appropriate acid chloride was slowly added. The reaction mixture was refluxed for four hours, cooled and shaken with 100 ml. of a saturated sodium bicarbonate solution. The benzene layer was dried with Drierite and the solvent removed. The residue was recrystallized or distilled, yielding the acyl derivatives (VII).

To the magnesium derivative of certain β-iminonitriles (0.1 mole) prepared as described above was added 0.2 mole of acetic anhydride, the ether replaced by 50 ml. more of acetic anhydride, and the mixture refluxed for three hours. After removing the excess anhydride under reduced pressure, the residue was washed with a saturated sodium bicarbonate solution and extracted with ether. The acyl derivative (VII) was isolated from the ether extract in the usual manner.

The results are summarized in Table II.

Cyclizations of acyl derivatives. To a suspension of 0.05 mole of sodium amide in liquid ammonia was added 0.02 mole of the acyl derivative (VII) in 50 ml. of dry dioxane. The liquid ammonia was replaced by 50 ml. more of dioxane and the mixture refluxed for three hours. After cooling, a solution of 3 g. of ammonium chloride in 25 ml. of water was added, and the mixture was evaporated under reduced pressure until a solid began to separate. Water was added until no more solid separated and the solid was recrystallized yielding the 2-hydroxy-4-aminopyridine. The results are given in Table III.

SUMMARY

Typical nitriles having α-hydrogen have been self-condensed by certain basic reagents in refluxing ethyl ether to form β-iminonitriles (dimers) and in refluxing *n*-butyl ether to form pyrimidine or pyridine types of cyclic trimers.

The mixed condensation between benzonitrile and phenylacetonitrile was effected with sodium amide.

The magnesium derivatives of β-iminonitriles were acylated with acid chlorides or anhydrides and the resulting acyl derivatives were cyclized by sodium amide to form 2-hydroxy-4-aminopyridines.

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