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DERIVATIVES OF 2-PYRIDONE

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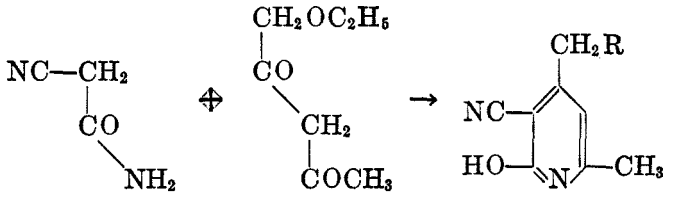
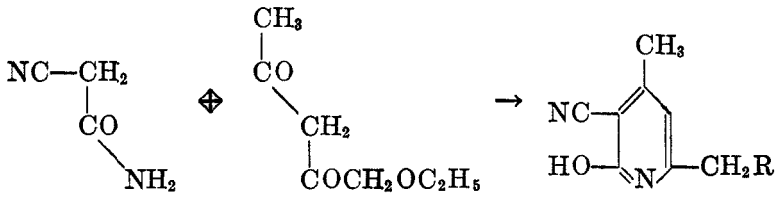
The chemistry of the 2-pyridones has long been a subject of great interest in the preparation of pharmaceuticals, and it has gained still greater prominence since the advent of Vitamin B_6. In the synthesis of 2-pyridones the pyridine ring system is frequently synthesized from suitable aliphatic compounds.

In the case of Vitamin B_6, the most convenient procedure consists in the reaction of cyanoacetamide (I) and ethoxyacetylacetone (II) leading to the formation of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (IIIa).[1]



I II IIIa R = OC_2H_5; IIIb R = OCH_3; IIIc R = H

The condensation is effected in the presence of an amine such as piperidine. Theoretically the condensation can also occur in an alternative way illustrated by the equation:

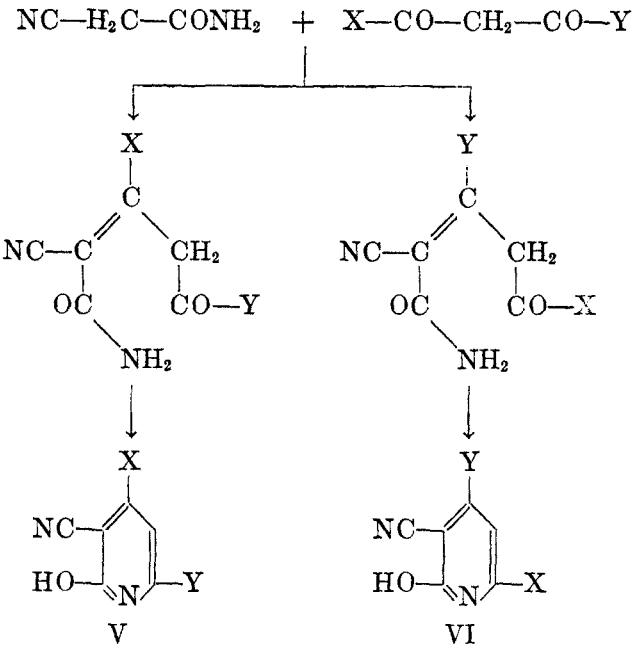


I II IVa R = OC_2H_5; IVb R = OCH_3

The mechanism of the reaction has been studied by Bardhan (1) with cyanoacetamide and several 1,3-diketones. He produced evidence that the formation

[1]For convenience, the formulas of the various pyridine derivatives are written in the aromatic form.

of the pyridine derivatives proceeds through unsaturated intermediates as illustrated by the scheme



He postulated that the relative reactivity of the respective carbonyl groups will determine the proportion of V and VI in the condensation product. The predominant isomer will have formula V if the carbonyl group adjacent to group X is more reactive and formula VI, if the more reactive carbonyl group is adjacent to Y. In the reaction of ethoxyacetylacetone with cyanoacetamide, both possible compounds IIIa and IVa are formed. Compound IIIa is isolated in about 75% yield, whereas compound IVa[2] is obtained in about 15% yield. If instead of ethoxyacetylacetone the lower homolog methoxyacetylacetone is used, the isomers IIIb and IVb are obtained in similar relative amounts.

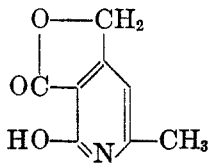
For the purpose of the synthesis of Vitamin B_6 the isomer IVa is a useless by-product. Since it is formed in considerable amounts, it seemed worth while to study its properties and reactions with the aim of obtaining useful derivatives. As a logical approach a study of the saponification and elimination of the cyano group was undertaken.

The behavior of the cyano group in compounds of the type of IIIa and IVa has not been investigated in detail. Harris, Stiller, and Folkers (2) found that compound IIIa is converted into the lactone VII by treatment with strong hydrochloric or sulfuric acid. It is therefore evident that the cyano group and the ethoxyl group are both attacked by acids.

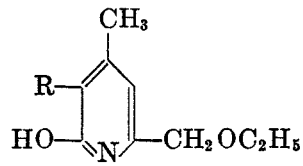
If the isomeric pyridone IVa is subjected to the action of mineral acids, no lactone can be formed. This reaction offers therefore the opportunity to study the relative susceptibility of the cyano group and the ethoxymethyl group to acid treatment. Refluxing compound IVa for five hours with 50% sulfuric acid gives

a mixture of compounds. As products of the reaction are found the acid VIIIa and the pyridone VIIIb, the former in about 5%, the latter in about 25% yield. A considerable quantity of the starting material, about 30%, is recovered unchanged. A further amount is completely broken down, apparently with splitting of the ethoxyl group.

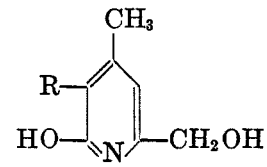
Fuming sulfuric acid reacts differently. At 5–10° the cyano group is largely unaffected, but the ethoxyl group is cleaved to give IXa. If, however, the reaction is carried out at 100°, the cyano group also undergoes saponification and the amide IXb is formed. Because this amide is rather soluble and difficult to isolate, it was converted by nitrous acid into the corresponding acid IXc which is easily isolated.



VII



VIIIa R = COOH
VIIIb R = H



IXa R = CN
IXb R = $CONH_2$
IXc R = COOH
IXd R = H

The results thus obtained are interesting because they illustrate that depending upon temperature and water content, sulfuric acid exerts a selective action on the cyano and ethoxyl groups in the same compound. However, acid treatment did not solve our original problem of converting the compound IVa into a uniform derivative with high yield.

We therefore resorted to the investigation of the action of alkali on the compound. The prospects of success were, however, not too great. Saponification of nitrile groups with alkalies is in general more difficult than with acids. In compounds of the type discussed here, the resistance of the cyano group is even more pronounced. The compound IIIc which is closely related to compounds IIIa and IVa having instead of the ethoxymethyl group a simple methyl group, has been subjected to the action of alkali by Moir (3). He found that even such drastic treatment as fusion with potash merely converted the cyano group into the amide group, yielding compound Xa. Since the ethoxymethyl group is less likely to survive such a treatment than a methyl group, fusion of either compound IIIa or IVa with alkali is obviously not too promising.

Compounds of the same type as IIIc, having a carboxyl group or a carbamyl group in place of the cyano group when subjected to alkaline treatment are not decarboxylated according to the results reported in the literature: Neither the amide Xa nor the ethyl ester Xb were decarboxylated with strong alkalies by Simonsen and Nayak (4) and by Knoevenagel and Cremer (5). These authors obtained only the corresponding free acid Xc.

In spite of these discouraging results we subjected compound IVa to the action of alkali for the following reasons. If the compound is written in the isomeric form XI, it can be regarded as a β-keto nitrile. Such nitriles when saponified give β-keto acids, which like acetoacetic acid, are known to undergo readily "ke-

TABLE I

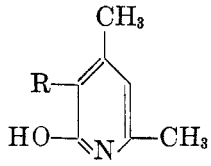
ALKOXYMETHYL-2-PYRIDONES

2-PYRIDONE DERIVATIVE	STRUCTURAL FORMULA	STARTING MATERIAL	REACTION TIME, HRS.	CRYSTAL'N SOLVENT	YIELD, %	M.P. °C	EMPIRICAL FORMULA	ANAL., %					
								Carbon		Hydrogen		Nitrogen	
								Calc'd	Found	Calc'd	Found	Calc'd	Found
4-Ethoxymethyl-6-methyl.....	XIIb	IIIa	24	Ethyl acetate	97	111–112	$C_9H_{13}NO_2$	64.65	64.72	7.84	7.72	8.38	8.55
4-Ethoxymethyl-6-methyl.....	XIIb	[a]	24	Ethyl acetate	92	109–110	$C_9H_{13}NO_2$						
4-Methyl-6-ethoxymethyl.....	XIIIb	IVa	36	Water	89	98–99	$C_9H_{13}NO_2$	Identical with material obtained in Part IIA					
4-Methoxymethyl-6-methyl...	XIIIb	IIIb	24	Ethyl acetate	88	129	$C_8H_{11}NO_2$					9.14	8.80
4-Methyl-6-methoxymethyl...	XIVb	IVb	24	Ethyl acetate	70	92	$C_8H_{11}NO_2$	62.72	62.41	7.24	7.19	9.14	9.19
4-Benzyloxymethyl-6-methyl..	XVb	XVa	28	Butanol	83	208–210	$C_{15}H_{14}N_2O_2$	70.85	70.87	5.55	5.88	11.02	11.08
4,6-Dimethyl.....		IIIc	41		74	172–173[b]	C_7H_9NO						
4-Hydroxymethyl-6-methyl...	XVIb	VII	8	Ethyl alcohol	42	213–214	$C_7H_9NO_2$	60.42	60.90	6.52	6.41	10.07	10.20
4-Methyl-6-hydroxymethyl...	IXd	IXa	24	Ethyl alcohol	37	224	$C_7H_9NO_2$	60.42	60.04	6.52	6.41	10.07	10.18

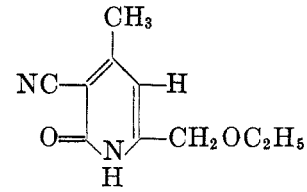
[a] 3-Carbamyl-4-ethoxymethyl-6-methyl-2-pyridone, prepared according to Schnider (7).

[b] This melting point is that of the unpurified product. Moir (3) reported the m.p. 177–179° (corr.).

tonic" cleavage not only with acids but also with dilute alkalies. Under proper conditions IVa should react similarly.



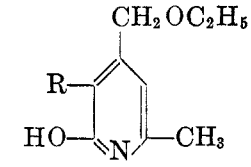
Xa R=$CONH_2$
Xb R=$COOC_2H_5$
Xc R=COOH



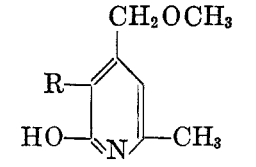
XI

Dilute aqueous alkali, at room temperature as well as at the boiling point, scarcely attacks the compound IVa. It is recovered practically quantitatively, even when boiled for several hours. If, however, the temperature is raised above 100°, by heating in an autoclave, saponification is achieved. If the compound is heated with dilute alkali at 150–170° for three to five hours, the acid VIIIa is formed. Continued heating for periods of 24 to 36 hours effects complete decarboxylation, yielding compound VIIIb. Both reactions proceed with excellent yields, and in spite of the high temperature practically no decomposition occurs. This reaction therefore is much superior to acid treatment, and fulfills the requirements for the technical problem confronting us.

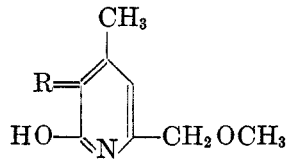
The success with compound IVa led to the investigation of the behavior of other 2-pyridones in the same reaction. The intermediate in the Vitamin B_6 synthesis, compound IIIa, likewise is saponified or decarboxylated under these conditions affording compounds XIIa and XIIb respectively. The corresponding methyl ethers IIIb and IVb are converted into the compounds, XIIIa and XIIIb, and XIVa and XIVb respectively. The benzyl ether XVa gives the pyridone XVb. The lactone VII is converted first into the acid XVIa and then into the compound XVIb. In this particular case, the acid XVIa is, however, more easily prepared by heating the lactone VII for a short time with dilute alkali at 100°. The nitrile IXa when heated for 20 hours with 5% sodium hydroxide at 160–170° yields compound IXd.



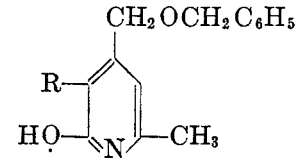
XIIa R=COOH
XIIb R=H



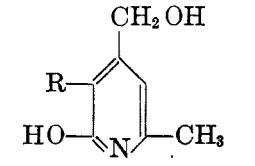
XIIIa R=COOH
XIIIb R=H



XIVa R=COOH
XIVb R=H



XVa R=CN
XVb R=H



XVIa R=COOH
XVIb R=H

With the compounds XVIb and IXd the yield is lower, because the hydroxymethyl groups are less resistent to the hot alkali than the corresponding alkoxyl groups in the other compounds.

The reaction proceeds equally well with all other functional derivatives of the carboxylic group. Thus, esters and amides react in the same way, yielding the free carboxylic acids or the decarboxylated derivatives in high yields when treated in the described manner.

The compounds obtained represent a new class of 2-pyridone derivatives which are easily accessible. They offer several opportunities for the preparation of derivatives which are at present under investigation.

We wish to thank Dr. Al Steyermark for the microanalyses recorded in the experimental part of this communication.

EXPERIMENTAL[3]

Part I. Preparation of 3-Cyano-2-Pyridones

Reaction of cyanoacetamide with alkoxy-1,3-diketones. A. *With ethoxyacetylacetone.* The condensation was carried out as described by Harris, Stiller, and Folkers (2) who reported however, only the compound IIIa, 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone. By acidification and concentration of the mother liquors about 15% of the isomeric 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa), m.p. 130°, can also be obtained.[2]

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58.
Found: C, 62.23; H, 6.29; N, 14.71.

B. *With methoxyacetylacetone.* Bruce and Coover (6) describe this condensation in detail. In our laboratory similar conditions gave not only the 3-cyano-4-methoxymethyl-6-methyl-2-pyridone (IIIb) described by them, but also the isomeric 3-cyano-4-methyl-6-methoxymethyl-2-pyridone (IVb), m.p. 152°, which was isolated from the mother liquors and crystallized from ethyl acetate.

Anal. Calc'd for $C_9H_{10}N_2O_2$: N, 15.72. Found: N, 15.49.

C. *With benzyloxyacetylacetone.* 1. *Ethyl benzyloxyacetate.* Twenty-three grams of sodium was stirred at room temperature in 500 g. of benzyl alcohol for 20 hours. To the solution 123 g. of ethyl chloroacetate was slowly added. The mixture was then warmed for several hours at 80°. After cooling, it was extracted with water to remove inorganic salt and then fractionated. At 205–207°/12 mm. ethyl benzyloxyacetate distilled as an oil.

2. *Benzyloxyacetylacetone.* Seven grams of sodium was pulverized in 100 cc. of xylene and 18 cc. of absolute alcohol was added slowly with stirring. After completion of the formation of sodium alcoholate, a mixture of 56 g. of ethyl benzyloxyacetate and 20 cc. of dry acetone was added with stirring. The mixture was stirred for 15 hours at room temperature. It was extracted with water and dilute sodium hydroxide. The combined extracts were acidified with dilute HCl and extracted with ether. The ether extract was dried over Na_2SO_4, evaporated, and the residue distilled in a high vacuum. Benzyloxyacetylacetone was obtained as a yellow oil of b.p. 115–120°/0.05 mm.; yield 40 g.

3. *3-Cyano-4-benzyloxymethyl-6-methyl-2-pyridone (XVa).* Thirty-three grams of benzyloxyacetylacetone, 18 g. of cyanoacetamide and 10 cc. of piperidine were dissolved in 100 cc. of alcohol. The mixture was stirred at room temperature for several hours and then warmed to 50°. After cooling, water and dilute HCl were added. The crystals were

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[2]This compound was first isolated by Dr. O. Schnider of the Hoffmann-La Roche laboratories in Basle, Switzerland. (Private communication.)

[3]All melting points are uncorrected.

scarely soluble in alcohol. They were purified by recrystallization from butanol; m.p. 208–210°; yield 25 g.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02.
Found: C, 70.87; H, 5.88; N, 11.08.

Part II. Action of Sulfuric Acid on 3-Cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa)

A. *Treatment of IVa with 50% sulfuric acid.* A mixture of 250 g. of IVa and 1250 cc. of 50% (by weight) sulfuric acid was refluxed for 5 hours and poured into 3700 g. of cracked ice. After the ice had melted, the precipitate was filtered and stirred with dilute sodium bicarbonate solution. The undissolved unchanged starting material was separated by filtration and dried; weight 82 g. Acidification of the filtrate with hydrochloric acid gave 9.9 g. of crude 3-carboxy-4-methyl-6-ethoxymethyl-2-pyridone (VIIIa) which was crystallized from water. The pure compound melted at 177–179°.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63.
Found: C, 56.89; H, 6.11; N, 6.81.

The sulfuric acid filtrate was treated with powdered sodium carbonate until *p*H 8.0 was reached. The resulting precipitate was filtered, digested with 250 cc. of boiling ethyl acetate, and filtered hot. On cooling, the filtrate gave 60 g. of crude 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb). On crystallization from water the pure substance, m.p. 101–102°, was obtained.

Anal. Calc'd for $C_9H_{13}NO_2 \cdot \frac{1}{2}H_2O$: C, 61.34; H, 8.01; N, 7.95.
Found: C, 61.41; H, 7.97; N, 8.42.

B. *Treatment of IVa with cold fuming sulfuric acid.* To 170 g. of fuming sulfuric acid (15% SO_3), cooled in an ice-bath, 30 g. of IVa was added with stirring at 5–10° in 25 minutes. The mixture was removed from the ice-bath, stirred for 1.5 hours, and poured into a mixture of 200 g. of ice and 300 cc. of water. The mixture was filtered and the filtrate allowed to stand overnight. The solution was warmed on the water-bath for one hour and then allowed to crystallize. The yield of 3-cyano-4-methyl-6-hydroxymethyl-2-pyridone (IXa) amounted to 21 g. After crystallization from water it melted at 224–227° d.

Anal. Calc'd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07.
Found: C, 59.06; H, 4.79; N, 16.68.

C. *Treatment of IVa with hot fuming sulfuric acid.* To 165 g. of fuming sulfuric acid (15% SO_3), 30 g. of IVa was added with stirring so that the temperature did not exceed 100°. The mixture was then heated at 95–100° for 30 minutes and poured into 200 g. of ice. A solution of 9.9 g. of sodium nitrite was introduced with stirring at 5–15° during 45 minutes. The solution was then heated at 95° until gas evolution ceased. On dilution with 400 cc. of water, 15 g. of crude 3-carboxy-4-methyl-6-hydroxymethyl-2-pyridone (IXc) was obtained. The pure compound, m.p. 223–224° d., was obtained by crystallization from water.

Anal. Calc'd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65; neutral equivalent 183.
Found: C, 53.13; H, 5.05; N, 7.75; neutral equivalent 184.

Part III. Preparation of 3-Carboxy-2-pyridones

A. These compounds are generally prepared by heating in an autoclave at about 170° from 3 to 5 hours a mixture of 1 part sodium hydroxide, 2 parts of a 3-cyano-2-pyridone, and 7 parts of water. The solution is acidified with cooling with hydrochloric acid until precipitation is complete. The precipitate is stirred with a saturated aqueous solution of sodium bicarbonate and filtered to remove the insoluble unchanged starting material. The filtrate is then acidified with hydrochloric acid to give the crude 3-carboxy-2-pyridone which may be crystallized from alcohol or purified by crystallization of the sodium salt.

B. *3-Carboxy-4-methyl-6-ethoxymethyl-2-pyridone (VIIIa).* This compound was obtained after subjecting 40 g. of the 3-cyano compound (IVa) to the above alkaline treatment (Part IIIA) for 5 hours. The crude acid was dissolved in 200 cc. of 4% sodium hydroxide solution, and 1300 cc. of acetone was then added; yield 33 g. of the crystal-

line sodium salt. Acidification of a solution of the sodium salt gave the free acid (VIIIa) m.p. 176–177°. It gave no depression in melting point when mixed with the product obtained by treatment of IVa with 50% sulfuric acid (Part IIA).

C. *3-Carboxy-4-ethoxymethyl-6-methyl-2-pyridone (XIIa).* The ester, m.p. 132° was first prepared in poor yield by the reaction of ethyl cyanoacetate and ethoxyacetylacetone in the presence of piperidine. On saponification it gave the acid (XIIa), which melted at 218–219° after crystallization from alcohol.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.21; N, 6.63.
Found: C, 57.01; H, 6.03; N, 6.47.

The same acid was obtained in much better yield by subjecting 40 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (IIIa) to the alkaline treatment in Part IIIA for 3 hours and 10 minutes; yield of crude product 31 g., m.p. 208–216°. After one crystallization from alcohol the product melted at 214–216°. It was identified by a neutral equivalent determination and by a mixed melting point with the product from the reaction of ethyl cyanoacetate and ethoxyacetylacetone.

Anal. Calc'd for $C_{10}H_{13}NO_4$: Neutral equivalent, 211. Found: Neutral equivalent, 216.

D. *3-Carboxy-4-methoxymethyl-6-methyl-2-pyridone (XIIIa).* When 60 g. of the 3-cyano compound (IIIb) was subjected to the alkaline treatment for 4 hours and 10 minutes, a yield of 49 g. of the 3-carboxy compound (XIIIa), m.p. 219–220° d., was obtained. Crystallization from alcohol gave the pure acid, m.p. 222–223° d.

Anal. Calc'd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62.
Found: C, 54.80; H, 5.60.

E. *3-Carboxy-4-methyl-6-methoxymethyl-2-pyridone (XIVa).* From 5.8 g. of 3-cyano-4-methyl-6-methoxymethyl-2-pyridone (IVb) there was obtained 5.0 g. of the crude 3-carboxy compound (XIVa) after 5 hours of the alkaline treatment described in Part IIIA. The compound was purified by crystallization from alcohol, m.p. 200–201°.

Anal. Calc'd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62.
Found: C, 54.54; H, 5.32.

F. *3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone (XVIa).* A mixture of 10 g. of the lactone (VII) and 100 cc. of 5% sodium hydroxide was boiled for a few minutes after solution had occurred. The solution was cooled in an ice-bath and slowly acidified with dilute hydrochloric acid. The precipitate was washed thoroughly with water and dried in a desiccator at room temperature; yield 10.7 g. The acid is soluble in sodium bicarbonate solution in contrast to the lactone which is insoluble in this reagent. When a sample was introduced into a melting point block at 250°, it melted with effervescence, resolidified and then melted again at about 300° with decomposition. This behavior varies with the rate of heating.

Anal. Calc'd for $C_8H_9NO_4$: Neutral equivalent, 186. Found: Neutral equivalent, 183.

Part IV. Elimination of the Cyano group or other Carboxylic Functional groups from the 3-position of 2-pyridones

The preparation of 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb) from the 3-cyano compound illustrates the general procedure for the preparation of all the compounds in Table I. With but two exceptions the 3-cyano compound was used as a starting material. The exceptions are the use of 3-carbamyl-4-ethoxymethyl-6-methyl-2-pyridone as a starting material for the preparation of 4-ethoxymethyl-6-methyl-2-pyridone (XIIb) and the use of the lactone VII for the preparation of 4-hydroxymethyl-6-methyl-2-pyridone (XVIb).

4-Methyl-6-ethoxymethyl-2-pyridone (VIIIb). A mixture of 90 g. of 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa), 45 g. of sodium hydroxide, and 315 cc. of water was heated in an autoclave at 170° for 36 hours. The mixture was cooled, acidified to *p*H 6–7, and filtered. A yield of 73 g. of 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb), m.p. 98–99°, was thus obtained. Its identity was established by a mixed melting point with the substance obtained by treatment of (IVa) with 50% sulfuric acid (Part IIA).

Alternatively the decarboxylated product can be extracted from the neutral reaction mixture with chloroform. The residue after distillation of the chloroform is then crystallized from the appropriate solvent.

SUMMARY

Condensation of cyanoacetamide with alkoxyacetylacetones occurs in two ways, yielding 4-alkoxymethyl-6-methyl-3-cyano-2-pryidones and 4-methyl-6-alkoxymethyl-3-cyano-2-pyridones. A method is described whereby these compounds are saponified or decarboxylated in high yields.

NUTLEY, N. J.

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