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The Cyclization of Malononitrile and Ketones by Ammonium Acetate

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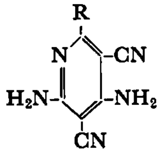
Hitherto various heterocyclic compounds have been synthesized by the reaction of ketones with ethyl cyanoacetate or ethyl acetoacetate in the presence of excessive ammonium acetate. On the basis of these facts, the reaction of malononitrile with ketones by ammonium acetate was carried out; aminopyridine derivatives, such as 2, 4-diamino-3, 5-dicyano-6-alkylpyridines (I) and 2-amino-3-cyano-4, 6-dialkylpyridines (II), were thus obtained.

Some active methylene compounds give heterocyclic compounds containing one nitrogen atom by condensation with ketones in the presence of ammonium acetate. Thus, ethyl cyanoacetate gives hydroxypyridines,[1] and ethyl acetoacetate gives hydroxyquinoline derivatives.[2]

The present paper will deal with the synthesis of aminopyridine derivatives by the condensation of malononitrile and various ketones (methyl ketones and α, β-unsaturated ketones) in the presence of ammonium acetate.

Condensations between aliphatic methyl ketones and malononitrile were carried out in a 1 : 2 molar ratio; 2, 4-diamino-3, 5-dicyano-6-alkylpyridines were thus obtained, with the elimination of one mole each of methane and water, as is indicated in the following scheme:

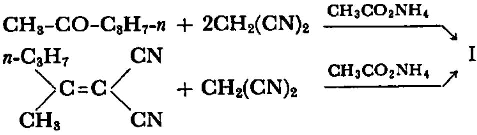
$$CH_3\text{-}CO\text{-}R + 2CH_2(CN)_2 \xrightarrow{CH_3CO_2NH_4}$$



I

a $R=CH_3$ b $R=C_2H_5$ c $R=n\text{-}C_3H_7$
d $R=n\text{-}C_5H_{11}$ e $R=n\text{-}C_6H_{13}$ f $R=n\text{-}C_9H_{19}$
g $R=i\text{-}C_4H_9$

The structure of I was proved from the infrared spectra and NMR spectra, as is shown in Tables 2 and 3. Furthermore, Ic was also obtained by the condensation of 1-methylbutylidenemalononitrile with malononitrile in the presence of ammonium acetate. The two products were established as identical by the results of elemental analyses, their infrared spectra, and by the fact these a mixed-melting-point determination showed no depression.

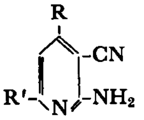


Ic

In the reaction with acetone, a compound (mp 340—342°C, $C_{14}H_{17}O_2N_5$) was obtained along with Ia. This compound was formed by the elimination of 1 mol each of methane, water, and hydrogen from 3 mol of acetone, 2 mol of malononitrile, and 1 mol of ammonia; it was also obtained by the use of mesityl oxide instead of acetone. Its structure could not be confirmed in this study.

α, β-Unsaturated ketones and malononitrile reacted in a 1 : 1 molar ratio to give 2-amino-3-cyano-4, 6-dialkylpyridines (II) through Michael reaction, with the elimination of 1 mol each of water and hydrogen.

$$R\text{-}CH{=}CH\text{-}CO\text{-}R' + CH_2(CN)_2 \xrightarrow{CH_3CO_2NH_4}$$



II

a $\{R=C_6H_5;\ R'=CH_3\}$ b $\{R=C_6H_5;\ R'=C_2H_5\}$
c $\{R=C_6H_5;\ R'=n\text{-}C_3H_7\}$ d $\{R=C_6H_5;\ R'=C_6H_5\}$

The hydrolysis of the cyano group of IId by heating with potassium hydroxide in alcohol gave an amide melting at 210—211°C; this amide was hydrolyzed to a carboxylic acid (III) by heating it with potassium hydroxide in glycerol. Compound III showed a mp of 233—234°C with decomposition. On the other hand, the reaction of ethyl cyanoacetate with benzalacetophenone in the presence of ammonium acetate[1] gave ethyl 2-amino-4, 6-diphenylnicotinate (IV). The carboxylic acid III was proved to be identical with the compound obtained by the hydrolysis of IV by the results of elemental analyses and by their infrared spectra.

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[1] A. Sakurai and H. Midorikawa, This Bulletin, **40**, 1680 (1967).

[2] A. Sakurai and H. Midorikawa, to be published.

TABLE 1. AMINOPYRIDINE DERIVATIVES OBTAINED BY THE REACTION OF MALONONITRILE WITH KETONES

Ketone	Product	Reaction time, hr	Mp °C	Crystn. solv.	Yield %	Formula	Calcd, %			Found, %		
							C	H	N	C	H	N
Acetone	Ia	3	336—338	Acetic acid	24	$C_8H_7N_5$	55.48	4.07	40.44	55.32	3.98	40.42
Methyl ethyl	Ib	5	304—306	Acetic acid	32	$C_9H_9N_5$	57.74	4.85	37.41	57.54	4.74	37.37
Methyl *n*-propyl	Ic	5	234—236	Acetic acid	34	$C_{10}H_{11}N_5$	59.68	5.51	34.81	59.44	5.29	34.82
Methyl *n*-amyl	Id	6	212—213	Acetic acid +methanol	21	$C_{12}H_{15}N_5$	62.86	6.60	30.55	62.92	6.17	29.96
Methyl *n*-hexyl	Ie	6	207—208	Methanol	25	$C_{13}H_{17}N_5$	64.17	7.04	28.79	64.47	6.72	28.46
Methyl *n*-nonyl	If	4	204—205	Alcohol +water	19	$C_{16}H_{23}N_5$	67.33	8.12	24.54	67.65	7.85	24.68
Methyl isobutyl	Ig	7	254—255	Methanol	4	$C_{11}H_{13}N_5$	61.37	6.09	32.54	61.56	5.61	32.36
Methyl styryl	IIa	5	235—236	Acetic acid +methanol	24	$C_{13}H_{11}N_3$	74.62	5.30	20.08	74.68	5.01	20.14
Ethyl styryl	IIb	3	197—199	Alcohol	34	$C_{14}H_{13}N_3$	75.31	5.87	18.82	74.94	5.56	19.24
Propyl styryl	IIc	7	150—151	Benzene	15	$C_{15}H_{15}N_3$	75.92	6.37	17.71	75.54	6.02	17.94
Phenyl styryl	IId	7	186—187	Alcohol	33	$C_{18}H_{13}N_3$	79.68	4.83	15.49	79.79	4.63	15.50

TABLE 2. IR SPECTRA OF AMINOPYRIDINE DERIVATIVES (KBr: cm^{-1})

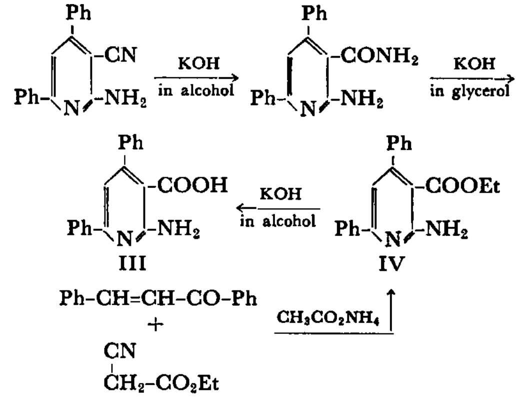
Compound	ν NH$_2$	ν C≡N (conj)	δ NH$_2$	ν C=C (conj)
Ia	3480, 3365, 3250, 3130 3340	2220 2200	1665 s, 1635 s	1560 s, 1490m
Ib	3480, 3380, 3240, 3110 3330	2220	1665 s, 1645 s	1565 s, 1490m
Ic	3470, 3380, 3240, 3120 3340	2210	1655 s, 1645 s	1560 s, 1490m
Id	3430, 3340, 3240, 3100	2225 2210	1665 s, 1640 s	1560 s, 1490m
Ie	3430, 3340, 3240, 3110 3320	2225 2205	1665 s, 1640 s	1565 s, 1490m
If	3420, 3320, 3230, 3090	2220 2200	1665 s, 1635 s	1560 s, 1490m
IIa	3400, 3320, 3160	2220	1650 s	1580 s, 1555 s, 1500m
IIb	3390, 3305, 3170	2210	1640 s	1580 s, 1555 s, 1500m
IIc	3400, 3305, 3130	2205	1650 s	1575 s, 1555 s, 1500m
IId	3470, 3310, 3180	2220	1640 s	1600w, 1590m, 1575 s 1550m, 1500m

s: strong m: medium w: weak

TABLE 3. NMR SPECTRA OF AMINOPYRIDINE DERIVATIVES IN CF$_3$CO$_2$H (ppm FROM TMS)

Compound	CH$_3$	CH$_2$	$=\overset{|}{C}H$	NH$_2$	C$_6$H$_5$
Ia	2.82 s			7.33 s, 7.50 s	
Ib	1.53 t	3.15 q		7.37 s, 7.55 s	
Ie	0.95 t	1.20—2.20m 3.10 t		7.35 s, 7.52 s	
IIa	2.80 s		7.15 s	7.25—7.55 br	7.72 s
IIb	1.50 t	3.05 q	7.12 s	7.25—7.50 br	7.70 s
IIc[a]	1.00 t	1.50—2.10m 2.70 t	6.67 s	5.55 s	7.50 s

a) in CDCl$_3$ s: singlet t: triplet q: quartet m: multiplet br: broad



The structure of II was supported by the infrared and NMR spectra, shown in Tables 2 and 3. The reaction with mesityl oxide did not give the expected product, but it was the same compound as that obtained by the reaction with acetone.

The reactions of malononitrile with acetophenone and cyclohexanone were abnormal, giving 3-cyano-5, 6-dihydro-4, 6-diphenyl-2-pyridone and 4-cyano-1, 5, 6, 7, 8, 8a-hexahydroisocarbostyryl-1-spiro-1'-cyclohexane respectively. The identities of these compounds with the substances obtained by the reactions of ethyl cyanoacetate with acetophenone and cyclohexanone respectively were supported by their melting points, and infrared spectra, and by the results of elemental analyses.

Experimental

All melting points are uncorrected.

The infrared spectra were determined by means of pressed potassium bromide disks.

The NMR spectra were determined in trifluoroacetic acid at a frequency of 60 Mc, using tetramethylsilane as an internal standard. The chemical shifts are given as ppm downfield from tetramethylsilane.

The Reaction of Malononitrile with Aliphatic Methyl Ketones. A mixture of malononitrile (0.1 mol), ketone (0.05 mol), and ammonium acetate (0.08 mol) was refluxed for 3—7 hr. From the solution a pale yellow, crystalline matter was then separated. The results are summarized in Table 1.

The Reaction of Malononitrile with 1-Methylbutylidenemalononitrile. A mixture of malononitrile (4.6 g, 0.07 mol), 1-methylbutylidenemalononitrile (9.4 g, 0.07 mol), and ammonium acetate (3.9 g, 0.05 mol) in 5 m*l* of alcohol was refluxed for 1.5 hr. After cooling, a crystalline matter separated; this was filtered and recrystallized from glacial acetic acid to give colorless crystals, mp 232—233°C. This compound was proved to be identical with Ic by a mixed-melting-point determination and by a study of its infrared spectrum.

Found: C, 59.42; H, 5.04; N, 35.00%. Calcd for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81%.

The Reaction with α, β-Unsaturated Ketones. A mixture of malononitrile (0.1 mol), ketones (0.1 mol), and ammonium acetate (0.8 mol) was refluxed in alcohol (15 m*l*) or without a solvent for 2—5 hr. After cooling, a crystalline matter precipitated; this was then worked up as usual. The results are summarized in Table 1.

Hydrolysis of 2-Amino-3-cyano-4, 6-diphenylpyridine (IId). Compound IId (2 g) was heated with 20% alcoholic potassium hydroxide (30 m*l*) for 5 hr. After the addition of water (20 m*l*) to the reaction mixture, it was left to stand overnight. The pale yellow crystals which precipitated were then recrystallized from alcohol to give 2-amino-3-carbamoyl-4, 6-diphenyl-pyridine, mp 210—211°C.

Found: C, 74.42; H, 5.00; N, 14.34%. Calcd for $C_{18}H_{15}ON_3$: C, 74.72; H, 5.23; N, 14.53%.

To a solution of potasium hydroxide (4 g) in glycerol (20 m*l*), 2-amino-3-carbamoyl-4, 6-diphenylpyridine (1 g) was added, and the mixture was boiled at 200°C for 5 hr. After cooling, the solution was neutralized with dilute hydrochloric acid; a crystalline solid separated, which was then recrystallized from methanol to afford 2-amino-3-carboxy-4, 6-diphenylpyridine, mp 232—234°C with decomposition. The results of elemental analyses and its infrared spectrum proved this substance to be identical with the compound obtained by the hydrolysis of ethyl 2-amino-4, 6-diphenylnicotinate.[1)]

Found: C, 74.06; H, 4.55; N, 9.29%. Calcd for $C_{18}H_{14}O_2N_2$: C, 74.48; H, 4.83; N, 9.66%.

The Reaction with Acetophenone. A mixture of malononitrile (3.3 g, 0.05 mol), acetophenone (6 g, 0.05 mol), and ammonium acetate (3.85 g, 0.05 mol) was heated for 7 hr. After standing overnight, the crystalline matter which was precipitated was recrystallized from alcohol to give 3-cyano-5, 6-dihydro-4, 6-diphenyl-6-methyl-2-pyridone, mp 213—214°C (lit.[3)] mp 213—214°C). This compound was identified with the compound obtained by the condensation of ethyl cyanoacetate and acetophenone by ammonium acetate.[1)]

Found: C, 79.11; H, 5.33; N, 9.85%. Calcd for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72%.

The Reaction with Cyclohexanone. A mixture of malononitrile (4.6 g, 0.07 mol), cyclohexanone (6.9 g, 0.07 mol), and ammonium acetate (5.4 g, 0.07 mol) was heated for 7 hr. After cooling, a crystalline matter separated; this was recrystallized from glacial acetic acid to afford 4-cyano-1, 5, 6, 7, 8, 8a-hexahydroisocarbostyryl-1-spiro-1'-cyclohexane, mp 244—246°C. By ts infrared spectrum and the results of elemental analyses, this compound was identified with the substance obtained by the reaction of ethyl cyanoacetate with cyclohexanone.[1)]

Found: C, 73.69; H, 8.05; N, 11.38%. Calcd for $C_{15}H_{20}ON_2$: C, 73.77; H, 8.20; N, 11.47%.

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3) S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).