Cyclic Amidines. Part XXII.[1] 1-Aryl-1,2-dihydro-2-iminopyridines

By **R. J. Grout, B. M. Hynam,** and **M. W. Partridge,*** The University, Nottingham

Interaction of ethyl 2-cyano-3-oxobutyrate and an arylamine salt yields a 1-aryl-5-cyano-1,2-dihydro-2-iminopyridine and an ethyl 3-arylamino-2-cyanocrotonate. The 1-aryl-2-iminopyridines are hydrolysed by water to 1-aryl-2-pyridones and with alkali undergo the Dimroth rearrangement to 2-arylaminopyridines. Ethyl 3-arylamino-2-cyanocrotonates are readily cyclised to 3-cyanoquinolines.

SYNTHESES of acyclic amidines have been extended to the production of 2-aminoquinolines.[2] The application of analogous reactions leading to the hitherto unknown 1-aryl-1,2-dihydro-2-iminopyridines is now reported.

Ethyl 2-cyano-3-oxobutyrate [3] and an arylammonium toluene-*p*-sulphonate at 160° gave a readily separable mixture of a 1-aryl-1,2-dihydro-2-iminopyridine (I; R = Ph, *p*-MeC_6H_4, *p*-$MeO{\cdot}C_6H_4$, or *p*-ClC_6H_4) and an ethyl 3-arylamino-2-cyanocrotonate (II; R = Ph, *p*-MeC_6H_4, *p*-$MeO{\cdot}C_6H_4$, or *p*-ClC_6H_4); with *p*-nitroanilinium toluene-*p*-sulphonate only the aminocrotonate (II; R = *p*-$O_2N{\cdot}C_6H_4$) was obtained. The structure assigned

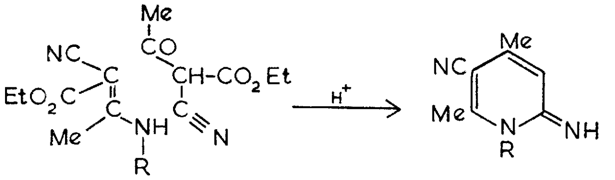
---

[1] Part XXI, H. G. Dean, R. J. Grout, M. W. Partridge, and H. J. Vipond, *J. Chem. Soc.* (*C*), 1968, 142.

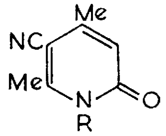
[2] R. Hardman and M. W. Partridge, *J. Chem. Soc.*, 1954, 3878; 1955, 510; 1958, 614.

[3] I. Hori and H. Midorikawa, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1962, **56**, 216 (*Chem. Abs.* 1963, **58**, 3311).

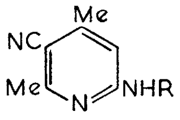
to the dihydropyridine (I; R = Ph) followed from its hydrolysis by boiling water to the corresponding pyridone (III; R = Ph) and from its spectroscopic properties; its n.m.r. spectrum showed two methyl peaks as singlets at τ 7·92 and 7·80 and further peaks at τ 4·30 (1H, s, exchangeable), 3·72 (1H, s), and 2·6 (5H, m) and its i.r. spectrum showed $\nu_{max.}$ 2170 (C≡N), 3310 (NH), and 1640 (C=N) cm.$^{-1}$. Other 1,2-dihydro-2-iminopyridines were similarly hydrolysed to the pyridones (III; R = p-MeC_6H_4, p-$MeO{\cdot}C_6H_4$, or p-ClC_6H_4); these showed i.r. spectral bands at 1680—1690 (CO) and 2180—2210 (CN) cm.$^{-1}$. As expected, the aminocrotonate (II; R = Ph) exhibited i.r. bands for NH and hydrogen-bonded carbonyl.



(II) (I)



(III)



(IV)

The aminocrotonate (II; R = Ph) and ethyl 2-cyano-3-oxobutyrate, with toluene-p-sulphonic acid, yielded the 1,2-dihydro-2-iminopyridine (I; R = Ph), but, in contrast to the cyclisation of β-aminocrotononitrile[4] to 2-amino-5-cyano-4,6-dimethylpyridine, no 1,2-dihydro-2-iminopyridine was detectable when this aminocrotonate (II; R = Ph) was heated at 160°, alone or with toluene-p-sulphonic acid. Accordingly, it seems probable that, in the formation of the 1-aryl-1,2-dihydro-2-iminopyridine (I) from an arylammonium toluene-p-sulphonate and ethyl 2-cyano-3-oxobutyrate, aminocrotonate (II) formation preceded the steps involving elimination of ethoxycarbonyl, condensation, and amidine formation. At 250—260°, the aminocrotonates (II; R = Ph, p-MeC_6H_4, p-$MeO{\cdot}C_6H_4$, p-ClC_6H_4, or p-O_2N-C_6H_4) behaved similarly to 3-arylamino-2-ethoxycarbonylacrylates[5] to give 3-cyanoquinolines in good yield.

Use of the potentially more reactive t-butyl 2-cyano-3-oxobutyrate[6] in the foregoing reaction did not increase the yield of 1,2-dihydro-2-iminopyridine (I; R = Ph). Replacement of the arylamine salt with ammonium toluene-p-sulphonate gave a low yield of the aminopyridine (IV; R = Ph), but with the n-butylammonium salt, no pyridine derivative was obtained. In the absence of toluene-p-sulphonic acid, ethyl 2-cyano-3-oxobutyrate acetylated aniline.

Failure of 5-cyano-1,2-dihydro-2-imino-1-methylpyridine to undergo a Dimroth rearrangement in alkali has been ascribed[7] to the electron-withdrawing effect of the cyano-group being insufficient to facilitate isomerisation. Evidently the augmentation of this effect by a 1-aryl substituent is adequate, since 1-aryl-5-cyano-1,2-dihydro-2-iminopyridines were readily isomerised by alkali to 2-arylaminopyridines (IV; R = Ph, p-MeC_6H_4, p-$MeO{\cdot}C_6H_4$, or p-ClC_6H_4). The n.m.r. spectrum of the p-chlorophenyl derivative was consistent with the structure (IV; R = p-ClC_6H_4), having two methyl peaks at τ 7·65 and 7·45, and signals for four aromatic protons at τ 2·7, an exchangeable proton at τ 3·10, and a pyridine proton at τ 3·55 (s).

EXPERIMENTAL

The n.m.r. spectra were obtained with a Perkin-Elmer R10 spectrometer operating at 60 Mc./sec. for solutions in deuteriochloroform with tetramethylsilane as internal standard.

*Interaction of Anilinium Toluene-*p*-sulphonate and Ethyl 2-Cyano-3-oxobutyrate.*—The melt obtained when anilinium toluene-p-sulphonate (53 g.) and ethyl 2-cyano-3-oxobutyrate (62 g.) were heated together at 160° for 90 min. was digested in boiling acetone (120 ml.) and gave 5-*cyano-1,2-dihydro-2-imino-4,6-dimethyl-1-phenylpyridinium toluene-*p*-sulphonate* (18·5 g., 24%) which gave needles, m.p. 257—260° (from n-butanol) (Found: C, 64·0; H, 5·5; N, 10·5. $C_{21}H_{21}N_3O_3S$ requires C, 63·8; H, 5·4; N, 10·6%). The *base* separated from benzene–light petroleum (b.p. 100—120°) as prisms, m.p. 141—142° [Found: C, 74·9; H, 5·6; N, 19·0%; M (potentiometric titration), 224. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%; M, 223]. Evaporation of the acetone mother liquor and crystallisation of the residue from aqueous ethanol afforded *ethyl* 3-*anilino-2-cyanocrotonate* (14·2 g., 36%) as prisms, m.p. 83—84°, $\nu_{max.}$ (CCl_4) 1660 (CO, hydrogen-bonded) and 2950—3200 (NH) cm.$^{-1}$, (Found: C, 67·3; H, 6·4; N, 11·8. $C_{13}H_{14}N_2O_2$ requires C, 67·8; H, 6·1; N, 12·2%).

A reaction time of 18 hr. gave 14% of the dihydropyridine and with t-butyl 2-cyano-3-oxobutyrate the yield of the dihydropyridine was 17%. When ethyl 3-anilino-2-cyanocrotonate (1 mol. of which 63% was recovered), ethyl 2-cyano-3-oxobutyrate (1 mol.), and toluene-p-sulphonic acid (1 mol.) were heated at 160° for 1 hr., the yield of dihydropyridine was 18%; at 210°, no recognisable product was obtained.

Dihydropyridines and *ethyl arylaminocrotonates* recorded in Tables 1 and 2 were similarly prepared.

3-*Cyano-2,4-dimethyl-1-phenyl-6-pyridone.*— 5-Cyano-1,2-dihydro-2-imino-4,6-dimethyl-1-phenylpyridine (0·5 g.) was boiled in water until ammonia ceased to be evolved (6 hr.). The precipitated *pyridone* (0·3 g.) formed plates, m.p. 166—167° [from benzene–light petroleum (b.p. 100—120°)] (Found: C, 75·1; H, 5·3; N, 12·1. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%).

The following 1-arylpyridones were prepared similarly:

---

[4] E. Bullock and B. Gregory, *Canad. J. Chem.*, 1965, **43**, 332.

[5] R. G. Gould, jun. and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890.

[6] H. Dahn and H. Hauth, *Helv. Chim. Acta*, 1959, **42**, 1214.

[7] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1965, 5542.

3-*cyano*-2,4-*dimethyl*-1-p-*tolyl*-6-*pyridone* (70%), plates, m.p. 240—241° [from benzene–light petroleum (b.p. 100—120°)] (Found: C, 75·7; H, 5·6; N, 11·9. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·9; N, 11·8%); 3-*cyano*-1-p-*methoxyphenyl*-2,4-*dimethyl*-6-*pyridone* (58%), prisms, m.p. 169—170° [from benzene–light petroleum (b.p. 100—120°)] (Found: C, 70·5; H, 5·6; N, 10·9. $C_{15}H_{14}N_2O_2$ requires C, 70·9; H, 5·6; N, 11·0%); and 1-p-*chlorophenyl*-3-*cyano*-2,4-*dimethyl*-6-*pyridone*, prisms, m.p. 243—244° [from benzene–light petroleum (b.p. 100—120°)] (Found: C, 64·9; H, 4·3; N, 10·8. $C_{14}H_{11}ClN_2O$ requires C, 65·0; H, 4·3; N, 10·8%).

TABLE 1

1-Aryl-5-cyano-1,2-dihydro-2-iminopyridines (I)

R	Yield (%)	M.p.	Solvent for recryst.*	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-MeC$_6$H$_4$		196—197°	A	75·6	6·3	17·3	$C_{15}H_{15}N_3$	75·9	6·4	17·7
toluene-*p*-sulphonate	24	233—235	B	64·0	5·6	10·4	$C_{22}H_{23}N_3O_3S$	64·5	5·7	10·3
p-MeO·C$_6$H$_4$		240—241	A	71·0	6·0	16·6	$C_{15}H_{15}N_3O$	71·1	6·0	16·6
toluene-*p*-sulphonate	34	226—230	B	62·1	5·5	9·9	$C_{22}H_{23}N_3O_4S$	62·2	5·5	9·9
p-ClC$_6$H$_4$		179—180	C	65·1	4·3	16·1	$C_{14}H_{12}ClN_3$	65·2	4·7	16·3
toluene-*p*-sulphonate	13	280—284	B	58·7	4·6	10·2	$C_{21}H_{20}ClN_3O_3S$	58·7	4·7	9·8

* A, benzene–light petroleum (b.p. 80—100°); B, water; C, aqueous ethanol.

TABLE 2

Ethyl 3-arylamino-2-cyanocrotonates (II)

R	Yield (%)	M.p.	Solvent for recryst.*	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-MeC$_6$H$_4$	28	109—110°	A	69·0	6·5	11·3	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·5
p-MeO·C$_6$H$_4$	36	115—117	B	64·2	6·2	10·7	$C_{14}H_{16}N_2O_3$	64·6	6·2	10·8
p-ClC$_6$H$_4$	39	147—148	B	59·2	4·9	10·6	$C_{13}H_{13}ClN_2O_2$	59·0	4·9	10·6
p-O$_2$N·C$_6$H$_4$	50	170—170·5	B	56·5	4·5	15·4	$C_{13}H_{13}N_3O_4$	56·7	4·8	15·3

* A, aqueous acetone; B, aqueous ethanol.

TABLE 3

6-Arylamino-3-cyano-2,4-dimethylpyridines (IV)

R	Yield (%)	M.p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-MeC$_6$H$_4$	57	160—161°	75·8	6·5	18·2	$C_{15}H_{15}N_3$	75·9	6·4	17·7
acetyl		112—113	72·9	5·8	15·4	$C_{17}H_{17}N_3O$	73·1	6·1	15·0
p-MeO·C$_6$H$_4$	45	140—141	71·5	5·8	16·7	$C_{15}H_{15}N_3O$	71·1	6·0	16·6
acetyl		97—98	69·1	5·9	14·3	$C_{17}H_{17}N_3O_2$	69·1	5·8	14·2
p-ClC$_6$H$_4$	63	179—180	65·1	4·5	16·1	$C_{14}H_{12}ClN_3$	65·2	4·7	16·3
acetyl		96—97	64·2	4·7	14·0	$C_{16}H_{14}ClN_3O$	64·1	4·7	14·0

6-Amino-3-cyano-2,4-dimethylpyridine.—Ammonium toluene *p*-sulphonate (3 g.) was recovered when this salt (3·8 g.) and ethyl 2-cyano-3-oxobutyrate (4·6 g.) were heated together at 160° for 5 hr. and digested with boiling chloroform (20 ml.). The chloroform solution was evaporated under reduced pressure and the residue, dissolved in water (charcoal) and basified with 2N-sodium hydroxide, gave the aminopyridine (0·2 g.), which separated from aqueous ethanol as needles, m.p. 225—226° (lit.,[4] 227—228°) (Found: C, 65·0; H, 6·1; N, 28·3. Calc. for $C_8H_9N_3$: C, 65·3; H, 6·2; N, 28·6%). The *picrate* gave needles, m.p. 252—252·5° (from dimethylformamide) (Found: C, 44·8; H, 2·8; N, 22·8. $C_{14}H_{12}N_6O_7$ requires C, 44·7; H, 3·2; N, 22·3%).

Interaction of Aniline and Ethyl 2-Cyano-3-oxobutyrate.—Aniline (1 mol.) and ethyl 2-cyano-3-oxobutyrate (1 mol.), heated together at 130—140° for 4·5 hr., furnished acetanilide (71%), m.p. and mixed m.p. 114°. Equimolecular quantities of aniline and the ester in ethanol at room temperature for 5 days furnished acetanilide (25%).

3-*Cyano*-4-*hydroxy*-2-*methylquinoline*.—Ethyl 3-anilino-2-cyanocrotonate (1 g.) was heated in boiling diphenyl ether (10 ml.) for 90 min.; the cooled solution deposited the *quinoline* (0·8 g.) which formed needles, m.p. 360—365° (decomp.) (from dimethylformamide) (Found: C, 71·4; H, 4·3; N, 15·1. $C_{11}H_8N_2O$ requires C, 71·7; H, 4·4; N, 15·2%).

The following quinoline derivatives were prepared in a similar manner from the appropriate ethyl 3-arylamino-2-cyanocrotonate: 3-*cyano*-4-*hydroxy*-2,6-*dimethylquinoline* (37%), plates, m.p. 345—360° (decomp.) (from dimethylformamide) (Found: C, 72·6; H, 4·8; N, 14·1. $C_{12}H_{10}N_2O$ requires C, 72·7; H, 5·1; N, 14·1%); 3-*cyano*-4-*hydroxy*-6-*methoxy*-2-*methylquinoline* (60%), prisms, m.p. 350—360° (decomp.) (from dimethylformamide) (Found: C, 66·9; H, 4·7; N, 13·3. $C_{12}H_{10}N_2O_2$ requires C, 67·3; H, 4·7; N, 13·1%); 6-*chloro*-3-*cyano*-4-*hydroxy*-2-*methylquinoline* (60%), prisms, m.p. 350—360° (decomp.) (from dimethylformamide) (Found: C, 60·7; H, 3·3; N, 13·1. $C_{11}H_7ClN_2O$ requires C, 60·4; H, 3·2; N, 12·8%); and 3-*cyano*-4-*hydroxy*-2-*methyl*-6-*nitroquinoline* (75%), yellow plates, m.p. 355—

360° (decomp.) (from dimethylformamide) (Found: C, 57·8; H, 3·2; N, 18·2. $C_{11}H_7N_3O_3$ requires C, 57·6; H, 3·1; N, 18·3%).

6-*Anilino*-3-*cyano*-2,4-*dimethylpyridine* was formed (1·3 g.) when 5-cyano-1,2-dihydro-2-imino-4,6-dimethyl-1-phenylpyridine (1·9 g.) was boiled under reflux in 2N-sodium hydroxide (50 ml.) for 2 hr. This *base* separated from aqueous ethanol as prisms, m.p. 134—135°, $\nu_{max.}$ (KBr) 2250 (C≡N) and 3370 (NH) cm.$^{-1}$ (Found: C, 75·4; H, 5·8; N, 18·9. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%). The *picrate* crystallised from n-butanol as needles, m.p. 206—208° (Found: C, 53·0; H, 3·5; N, 18·6. $C_{20}H_{16}N_6O_7$ requires C, 53·1; H, 3·6; N, 18·6%). Its *acetyl* derivative, formed in boiling acetic anhydride [conc. sulphuric acid (1 drop)], separated from aqueous ethanol as plates, m.p. 105—106°, $\nu_{max.}$ (KBr) 1695 (CO) and 2200 (C≡N) cm.$^{-1}$ (Found: C, 72·5; H, 5·4; N, 16·0. $C_{16}H_{15}N_3O$ requires C, 72·4; H, 5·7; N, 15·8%).

The *pyridines*, prepared similarly, are recorded in Table 3.

We thank Dr. H. Booth for the measurement of and discussions on the n.m.r. spectra, the S.R.C. for a studentship (to B. M. H.), and Smith, Kline and French (Philadelphia) for financial support.

[9/296 *Received, February* 19*th*, 1969]