709. *Heterocyclic Syntheses with Malonyl Chloride. Part VI.*[1] *3-Substituted Pyridine Derivatives from α-Methylene-nitriles.*

By S. J. Davis, J. A. Elvidge, and Arthur Brian Foster.

Acetonitrile condenses with malonyl chloride at room temperature, giving 2-chloro-4,6-dihydroxypyridine. Monosubstituted acetonitriles likewise yield the corresponding 3-substituted pyridine derivatives. Thus propionitrile gave 2-chloro-4,6-dihydroxy-3-methylpyridine; this was converted into the 2,4,6-trichloro-derivative and thence, by reduction, into 3-picoline.

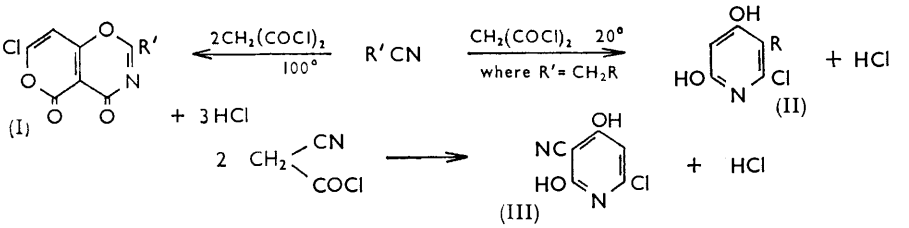
Bromomalonyl chloride with ethyl cyanoacetate yielded fully substituted 5-bromo-2-chloro-3-ethoxycarbonyl-4,6-dihydroxypyridine, but methylmalonyl chloride failed to condense with propionitrile.

Light absorptions and the mechanism of the new pyridine synthesis are discussed.

Nitriles interact rapidly at 100° with two molecular proportions of malonyl chloride to form chloropyrono-oxazines (I).[1] However, at room temperature, and with α-methylene-nitriles, only 1 mol. of malonyl chloride is consumed and the products are

[1] Part V, Davis and Elvidge, *J.*, 1962, 3553.

β-substituted chlorodihydroxypyridines (II), or tautomerides thereof, convertible into β-substituted pyridines. A preliminary account of this new pyridine synthesis follows.



A mixture of malonyl chloride and acetonitrile at room temperature slowly evolved hydrogen chloride and afforded a solid, m. p. 233°, which, in contrast to the compound (I) obtained at 100°,[1] was enolic and stable to cold alkali. These properties and the molecular composition $C_5H_4ClNO_2$ led to the identification of the new product as 2-chloro-4,6-dihydroxypyridine (II; R = H), a compound which Schroeter and Finck [2] had prepared from the cyanopyridine (III) by hydrolysis to the acid and decarboxylation.

The cyanopyridine (III) had earlier been isolated by Schroeter and Seidler [3] as a product of the self-condensation of cyanoacetyl chloride, a reaction with similarities to the one we had discovered. Whereas the extension of the cyanoacetyl chloride condensation to monosubstituted cyanoacetyl chlorides gave only products of high molecular weight,[4] we found that monosubstituted acetonitriles condensed with malonyl chloride analogously to acetonitrile itself. From propionitrile, γ-chlorobutyronitrile, valeronitrile, ethyl cyanoacetate, and benzyl cyanide, the 3-substituted 2-chloro-4,6-dihydroxypyridines (II) were readily obtained. The orientation of the substituents was demonstrated by transformations of the propionitrile and the ethyl cyanoacetate product.

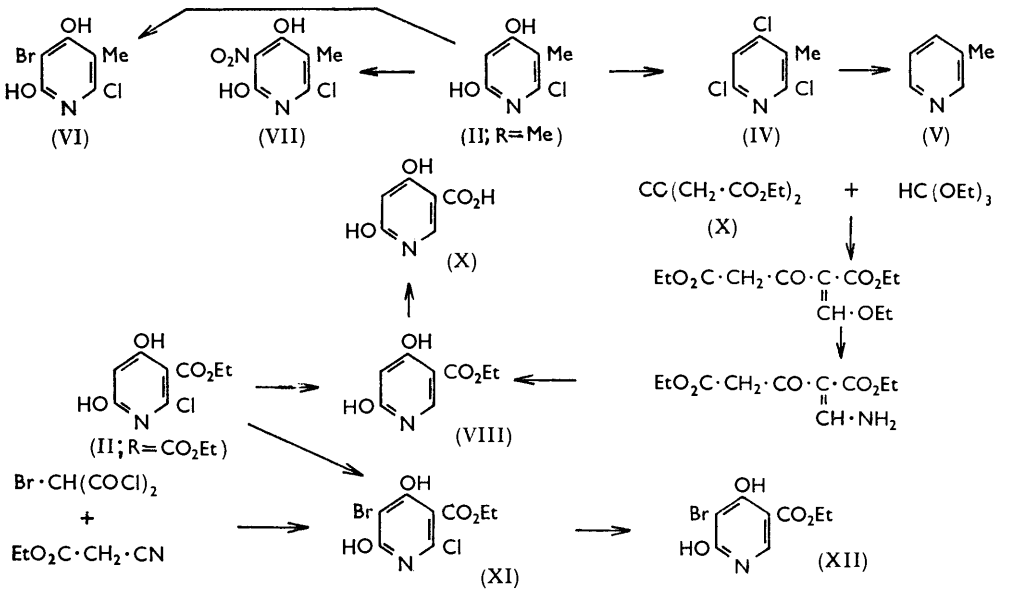
Vigorous treatment of the propionitrile product (II; R = Me) with phosphorus oxychloride effected replacement of the hydroxyl groups by chlorine and gave the methyl trichloropyridine (IV). As expected, this was smoothly dehalogenated by hydrogen and Raney nickel, giving β-picoline (V) which was characterised as the picrate. Further, it was shown that the free β-position in the propionitrile product (II; R = Me) was susceptible to electrophilic substitution, as bromination gave compound (VI) and nitration compound (VII).

It remained to demonstrate the orientation of the α-chlorine with respect to the β-substituent derived from the nitrile component in the malonyl chloride condensation. This was effected by reductive dehalogenation, with zinc and acid, of the ethyl cyanoacetate product (II; R = CO_2Et). The resulting ester, $C_8H_9NO_4$, and the derived carboxylic acid had melting points in agreement with those found by Errera [5] for the compounds (VIII) and (IX), respectively, which he prepared unambiguously from ethyl acetonedicarboxylate (X), as shown. Therefore, in the 3-substituted dihydroxypyridines (II), the chlorine occupied the 2- and not the 6-position.

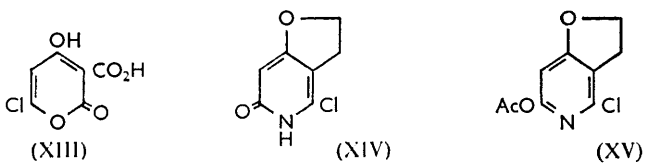
Attempts to employ substituted malonyl chlorides for the new pyridine synthesis met with limited success. Methylmalonyl chloride failed to react with propionitrile, but bromomalonyl chloride condensed smoothly with ethyl cyanoacetate, to yield the fully substituted pyridine (XI). The same product (XI) was obtained by brominating the ester (II; R = CO_2Et). Reduction of compound (XI) removed the α-chlorine and gave 3-bromo-5-ethoxycarbonyl-2,4-dihydroxypyridine (XII), identical with the known bromination product [6] of the dihydroxypyridine ester (VIII).

[2] Schroeter and Finck, *Ber.*, 1938, **71**, 671.
[3] Schroeter and Seidler, *J. prakt. Chem.*, 1922, **105**, 165.
[4] Schroeter, Seidler, Sulzbacher, and Kanitz, *Ber.*, 1932, **65**, 432.
[5] Errera, *Ber.*, 1898, **31**, 1682.
[6] den Hertog, *Rec. Trav. chim.*, 1945, **64**, 85.

In further experiments, the condensation of malonyl chloride with αω-dinitriles was attempted, but only the pyrone acid (XIII) was isolated from the reactions with succino- and glutaro-nitrile. Evidently these nitriles were sufficiently basic to induce the self-condensation of malonyl chloride,[7] to the exclusion of other possible reactions.



It appeared that bicyclic pyridine derivatives might be obtainable from the γ-chlorobutyronitrile product (II; R = $[CH_2]_2$·Cl) and also from analogous pyridines which the new synthesis would make accessible. However, attempts to cyclise the product (II;



R = $[CH_2]_2$·Cl) with ammonia, hydrazine, and phenylhydrazine, were disappointing in that each gave the same monodehydrochlorination product, $C_7H_6ClNO_2$. For this the only reasonable structure was (XIV) (or the lactim tautomer). Acetylation of this bicyclic product afforded the *O*-acetyl derivative (XV).

Light Absorption and Fine Structure.—The chlorodihydroxypyridines (II) and their substitution products showed absorption maxima in the 250—280 mμ region (Table 1), as expected of simple pyridine derivatives. However, it was not possible to decide from these data the preferred tautomeric form of each compound. den Hertog and Buurman [8] had shown by means of *O*- and *N*-methyl derivatives that the three conjugated tautomeric forms of 2,4-dihydroxypyridine had distinct ultraviolet absorption (see Table 1) and that the parent compound was best regarded as 4-hydroxy-2-pyridone. Presumably because of the extra substituents, none of the present compounds conformed unambiguously to any one of the three model types.

In the infrared region (Table 2), the propionitrile product (II; R = Me) showed O–H and N–H stretching in the 2·4—4·0 μ region, but no well-resolved band near 1660 or

[7] Elvidge, *J.*, 1962, 2606.
[8] den Hertog and Buurman, *Rec. Trav. chim.*, 1956, **75**, 257.

TABLE 1.

Ultraviolet absorptions.

Compound	Solvent	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$
(II; R = Me)	Dioxan	269	3·5
(II; R = Pr)	,,	270	3·3
(II; R = $[CH_2]_2$·Cl)	EtOH	280	3·5
(II; R = CO_2Et)	Dioxan	257	9·4
(II; R = Ph)	,,	256	7·0
(IV)	,,	275	4·5
(VI)	,,	275	4·0
(VII)	,,	270	3·7
(VIII)	,,	260	9·1
(XI)	,,	265	7·4
2-Methoxy-1-methyl-4-pyridone *	aq. EtOH (1 : 1)	250	12·6
2,4-Dimethoxypyridine *	,,	260	2·0
4-Methoxy-1-methyl-2-pyridone *	,,	280	4·0

* Ref. 8.

TABLE 2.

Infrared absorptions.

Compound	$\nu_{max.}$ (cm.$^{-1}$)
(II; R = Me) *	3356s, 3165, 2660sb, 1653sh, 1613s, 1592s, 1558sh, 1504w, 1439, 1397, 1379w, 1355, 1316, 1236s, 1186, 1056, 941b, 867, 848w, 831, 767, 716w
(II; R = Me) †	3344w, 3145, 2660b, 1653sh, 1613s, 1592s, 1550, 1499w, 1395w, 1314, 1238, 1186, 1062, 941sb, 907s, 831s, 768, 718
(XIV) †	2667b, 1653, 1603s, 1560w, 1333, 1292w, 1248, 1222, 1199s, 1185w, 1149s, 1005, 975 939w, 903sb, 815s, 787, 722wb, 688
(XV) †	1754s, 1613, 1587s, 1404w, 1304w, 1255, 1205s, 1172s, 1120s, 1015s, 992, 972w, 919s, 887, 834, 798w, 722w, 699w

* KBr disc. † Nujol mull.

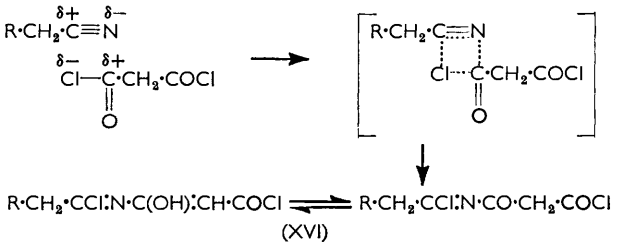
1575 cm.$^{-1}$ which are the carbonyl double-bond stretching frequencies for 2- and 4-pyridones, respectively.[9] However, if the shoulder at 1653 cm.$^{-1}$ is assigned to a 2-carbonyl group, then the remaining bands in the double-bond stretching region fit reasonably well with Katritzky and Jones's 2-series ring-stretching modes.[9] Not even an approximate correlation with these authors' data for the 4-series is obtained by starting from the alternative assumption that the strong absorption at 1592 cm.$^{-1}$ represents a 4-carbonyl stretch. On this limited evidence, the 4-hydroxy-2-pyridone tautomeric form is favoured for the propionitrile product (II; R = Me).

The bicyclic compound (XIV) showed a strong carbonyl band at 1653 cm.$^{-1}$, so that the 2-pyridone structure was indicated. It then followed that the broad absorption centred at 2667 cm.$^{-1}$ resulted from bonded N–H. In the spectrum of the acetyl derivative there was a strong band at 1754 cm.$^{-1}$, attributable to ester-carbonyl stretching, and no absorption in the 2-pyridone carbonyl region, so that the *O*-acetyl constitution (XV) was demonstrated.

Mechanism of the Pyridine Synthesis.—By following the reaction between malonyl chloride and propionitrile spectrophotometrically, the results in Table 3 were obtained. It appeared that the reaction occurred in two main stages. During the first 2 hr. the solution showed increasing absorption at about 257 mμ. Only subsequently did hydrogen chloride obviously appear in the reaction medium, and the characteristic absorption of the pyridine product (II; R = Me) at 269 mμ become detectable. It was evident from the absorption at 305 mμ of the final solution that self-condensation of some of the malonyl chloride had occurred [7,1] as a side reaction. In a parallel experiment it was found that an excess of bromide ion (added as lithium bromide, which is somewhat soluble in propionitrile) merely slowed the reaction; the product was still the chlorodihydroxypyridine (II; R = Me).

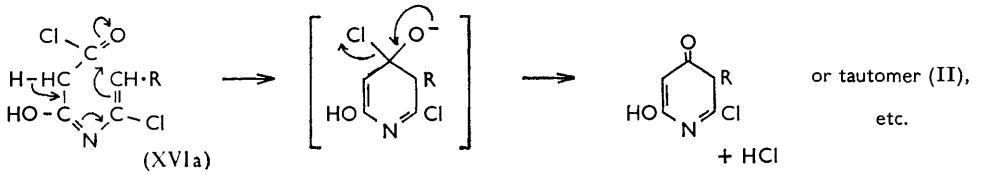
[9] Katritzky and Jones, *J.*, 1960, 2947.

The observations suggested that the new pyridine synthesis involved, first, addition of malonyl chloride to the nitrile to form the linear intermediate (XVI). This intermediate would be expected to be enolic and so to absorb light in the 250—260 mμ region, like sorbic acid [10] for example. The formation of (XVI) might start as an antiparallel association of nitrile and carbonyl chloride dipoles and proceed *via* a four-centre transition complex:



(XVI)

Cyclisation of this intermediate (XVI), best in the tautomeric form (XVIa), would then follow with elimination of hydrogen chloride:



(XVIa)

The important requirement for the first stage is evidently that the acid chloride should bear a powerful electron-withdrawing substituuent.

The alternative direction of ring synthesis, involving first the formation of the carbon–carbon 3,4-bond by acylation of the nitrile α-methylene group and then formation of the carbon–nitrogen 1,2-bond by ring closure between the nitrile and the carbonyl chloride group can be excluded. Hydrogen chloride would appear at the beginning of the reaction, the acyclic intermediate would have a chromophore of the glutaconic type, and the final cyclisation would be sterically awkward and would probably allow halogen exchange.

Experimental

3-Substituted 2-Chloro-4,6-dihydroxypyridines.—Malonyl chloride [11] was kept with the α-methylene-nitrile at room temperature (with exclusion of moisture), and the product was collected, washed with dioxan, and recrystallised. The experimental details are in the annexed Table.

In aqueous dioxan, these compounds gave pale orange colours with ferric chloride. Each was soluble in aqueous alkali and was recovered on neutralisation.

Conversion of 2-Chloro-4,6-dihydroxy-3-methylpyridine into β-Picoline.—The compound No. 2 (4·75 g.) and phosphorus oxychloride (30 c.c.) were heated at 180° for 24 hr. Steam-distillation of the mixture and cooling of the distillate afforded *2,4,6-trichloro-3-methylpyridine* (3·4 g., 58%), m. p. 28·5° (from ethanol) (Found: C, 37·4; H, 2·4; Cl, 52·65; N, 7·3. $C_6H_4Cl_3N$ requires C, 36·7; H, 2·0; Cl, 54·2; N, 7·1%).

This trichloro-compound (1 g.) in 0·4N-sodium hydroxide (60 c.c.) was hydrogenated over Raney nickel (1 g.) at 50°/5 atm. for 3 days. After filtration, the solution was neutralised with hydrochloric acid and extracted with ether (3 × 20 c.c.). The dried ($CaCl_2$) extract was evaporated and the residue treated with ethanolic picric acid. β-Picoline picrate (0·26 g.), yellow needles, had m. p. and mixed m. p. 150° (from ethanol) (Found: C, 44·5; H, 3·4. Calc. for $C_{12}H_{10}N_4O_7$: C, 44·75; H, 3·1%).

Substitution Reactions of 2-Chloro-4,6-dihydroxy-3-methylpyridine.—(*a*) Bromine (0·3 c.c.)

[10] Eisner, Elvidge, and Linstead, *J.*, 1953, 1372.
[11] Staudinger and Bereza, *Ber.*, 1908, **41**, 4463.

was added dropwise to a solution of compound No. 2 (0·5 g.) in ethanol (5 c.c.), and the mixture was refluxed for 1 hr. Addition of water precipitated *5-bromo-2-chloro-4,6-dihydroxy-3-methylpyridine* (VI), golden plates (0·65 g., 95%), m. p. 198° (from aqueous ethanol) (Found: C, 30·5; H, 2·3; N, 5·7. $C_6H_5BrClNO_2$ requires C, 30·2; H, 2·2; N, 5·9%).

No.	R in RCN	(c.c.)	Malonyl chloride (c.c.)	Reaction time	2-Chloro-4,6-dihydroxypyridine	Yield (g.)	Yield (%)
1	Me	5·25	9·75	3 days	(3-H)	3·4	(23)
2	Et	13·9	12·9	24 hr.	3-Methyl-	13·4	(63)
3	$Cl\cdot[CH_2]_2$	4·2	5·8	6 days	3-2′-Chloroethyl-	4·1	(48)
4	Bu	3·0	1·95	3 ,,	3-Propyl-	0·97	(26)
5	$EtO_2C\cdot CH_2$	3·75	6·4	6 ,,	3-Ethoxycarbonyl-	2·0	(33)
6	$Ph\cdot CH_2$	4·7	8·0	6 ,,	3-Phenyl-	4·7	(53)

				Found (%)					Reqd. or Calc. (%) *				
No.	Form (solvent)	M. p.	Formula	C	H	Cl	N	*M*	C	H	Cl	N	*M*
1	Laths (H_2O)	233° [2]	$C_5H_4ClNO_2$			24·45		148			24·35		146
2	Prisms (MeOH)	302°	$C_6H_6ClNO_2$	45·4	4·05	22·3	8·8		45·15	3·8	22·2	8·8	
3	Laminæ (EtOH)	257°	$C_7H_7Cl_2NO_2$	40·25	3·6	34·9	6·4		40·4	3·4	34·1	6·75	
4	Leaflets ($Ph\cdot NO_2$)	305°	$C_8H_{10}ClNO_2$	50·65	5·5	18·9	7·25		51·2	5·35	18·9	7·45	
5	Faintly yellow needles ($CN\cdot CH_2\cdot CO_2Et$)	219°	$C_8H_8ClNO_4$	44·15	3·95	16·0	6·5	225	44·15	3·7	16·3	6·45	218
6	Leaflets (PhCN)	310°	$C_{11}H_8ClNO_2$	59·6	3·9	16·0	6·2		59·6	3·65	16·0	6·3	

* Compounds 2—6 are new.

(*b*) Compound No. 2 (1 g.) was warmed with 50% nitric acid (10 c.c.) until the solution was deep red. The solution was then rapidly cooled and the product collected on a sintered-glass filter. From water, yellow needles of *2-chloro-4,6-dihydroxy-3-methyl-5-nitropyridine* (VII) (1·2 g., 94%), m. p. 233°, separated (Found: C, 34·8; H, 2·6; Cl, 17·15; N, 13·5. $C_6H_5ClN_2O_4$ requires C, 35·05; H, 2·5; Cl, 17·35; N, 13·65%).

Dehalogenation of 2-Chloro-3-ethoxycarbonyl-2,4-dihydroxypyridine.—Compound No. 5 (1g.), zinc dust (1·4 g.), and 2N-sulphuric acid (22 c.c.) were heated under reflux for 20 min., and the mixture was filtered and cooled, whereupon the product crystallised. From 2N-hydrochloric acid, the 3-ethoxycarbonyl-4,6-dihydroxypyridine (VIII) separated as leaflets (0·6 g., 71%), m. p. 218·5° (Found: C, 52·05; H, 5·3; N, 7·65. Calc. for $C_8H_9NO_4$: C, 52·4; H, 4·95; N, 7·65%). Errera [5] recorded m. p. 213°; den Hertog [6] found m. p. 219°.

Hydrolysis of the ester with hot 2N-sodium hydroxide for 1·5 min., acidification, and cooling, yielded the acid, m. p. 307° (decomp.). Errera [5] reported m. p. 310° (decomp.).

Condensation of Bromomalonyl Chloride with Ethyl Cyanoacetate.—Bromomalonyl chloride (7 g.; b. p. 27°/0·25 mm., n_D^{21} 1·5478), obtained by the action of thionyl chloride on bromomalonic acid,[12] was kept with ethyl cyanoacetate (2 c.c.) for 7 days in the absence of moisture. From aqueous dioxan, the *5-bromo-2-chloro-3-ethoxycarbonyl-4,6-dihydroxypyridine* (XI) (1·5 g., 28%) crystallised as plates, m. p. 238° (Found: C, 31·6; H, 2·4; Br, 26·6; Cl, 11·7; N, 4·3. $C_8H_7BrClNO_4$ requires C, 32·3; H, 2·4; Br, 26·9; Cl, 11·9; N, 4·7%). The same compound, m. p. and mixed m. p. 238°, was obtained by warming the 2-chloro-3-ethoxycarbonyl-4,6-dihydropyridine (No. 5) (1 g.) in dioxan (5 c.c.) with bromine (0·56 c.c.) in dioxan (5 c.c.) for 10 min., cooling, and adding water.

3-Bromo-5-ethoxycarbonyl-2,4-dihydroxypyridine (XII).—The preceding 2-chloro-compound (XI) (0·8 g.) in dioxan (5 c.c.) was boiled with zinc dust (1·2 g.) and 2N-sulphuric acid (20 c.c.) for 1 hr. The mixture was filtered and cooled, whereupon the product crystallised. Sublimation at low pressure then afforded 3-bromo-5-ethoxycarbonyl-2,4-dihydroxypyridine (0·21 g., 30%), m. p. 259—260° (decomp.) (Found: C, 37·3; H, 3·3. Calc. for $C_8H_8BrNO_4$: C, 36·7; H, 3·1%). den Hertog [6] gave the same m. p.

Attempted Condensation of Malonyl Chloride with Succinonitrile.—Malonyl chloride (6 g.) and succinonitrile (3·4 g.) were kept together for 7 days, with exclusion of moisture. The black mass was extracted with dioxan, and the solution was evaporated under reduced pressure

[12] Lutz, *Ber.*, 1902, **35**, 2549.

and treated with ether. The product (0·21 g.), which slowly separated as the solvent evaporated, gave a dark red colour with ferric chloride and crystallised from light petroleum (b. p. 80—100°) as needles, m. p. 135°, undepressed on admixture with 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid.[7]

2-Chloro-1,6,4′,5′-tetrahydro-6-oxofurano(3′,2′-3,4)pyridine (XIV).—(*a*) The compound No. 3 (0·5 g.) in ethanol (5 c.c.) was heated under reflux with aqueous ammonia (2 c.c.; *d* 0·88) and copper powder (0·5 g.) for 1 hr. The mixture was cooled in ice, then filtered, and the solid triturated with 2N-sodium hydroxide. The alkaline extract was filtered, neutralised with hydrochloric acid, and extracted with ether. On evaporation of the ether and crystallisation of the residue from ethanol, the *product* (XIV) (0·29 g., 71%) was obtained as needles, m. p. 264° (Found: C, 49·1; H, 3·8. $C_7H_6ClNO_2$ requires C, 49·0; H, 3·5%). In ethanol, it gave no colour with ferric chloride.

(*b*) With hydrazine hydrate (2 c.c.) or phenylhydrazine (2 c.c.) in place of ammonia in the preceding preparation, the same product (XIV) was obtained (0·33 g. 80%; 0·36 g., 85%, respectively), m. p. and mixed m. p.s 264°.

Acetyl Derivative (XV).—The bicyclic pyridone (XIV) (0·4 g.) was boiled with acetic anhydride (4 c.c.) for 1 hr., and the solution was then evaporated under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 60—80°) gave *6-acetoxy-2-chloro-4′,5′-dihydrofurano(3′,2′-3,4)pyridine* as needles, m. p. 95° (Found: C, 50·7; H, 4·1; N, 6·5. $C_9H_8ClNO_3$ requires C, 50·6; H, 3·8; N, 6·6%).

Spectrophotometric Study of the Reaction between Malonyl Chloride and Propionitrile.—A mixture of malonyl chloride (0·90 c.c.) and propionitrile (0·65 c.c.) was kept at room temperature, with exclusion of moisture. At intervals, a portion (9·6 mg.) was withdrawn and diluted with

TABLE 3.

Time (hr.)	$\lambda_{max.}$ (mμ)	$E^{1\%}_{1\,cm.}$	Time (hr.)	$\lambda_{max.}$ (mμ)	$E^{1\%}_{1\,cm.}$	Time (hr.)	$\lambda_{max.}$ (mμ)	$E^{1\%}_{1\,cm.}$
0·5	258	50	3·0	272	70	4·0	269	81
1·0	257	57		305	83		305	110
2·0	259	63				5·0	270	99
	266	67					305	160
	310	73						

ethanol (benzene-free) to 100·0 c.c., and the extinction measured with a Unicam S.P. 500 spectrophotometer (see Table 3). After 2 hr., fumes of hydrogen chloride appeared in the flask when the stopper was removed. At 5 hr., the extinction maxima corresponded to 45% of (II; R = Me) and 35% of malonyl chloride self-condensation product.

Interaction of Malonyl Chloride with Propionitrile in the Presence of Bromide.—Lithium bromide (1 g.; powdered and dried) was warmed with propionitrile (2·6 c.c.), the solution was cooled rapidly, and malonyl chloride (2 c.c.) was added. After 5 days (with exclusion of moisture), the solid product was triturated with dioxan, collected, washed with dioxan, and then triturated with water, and collected. The dried product (1 g.), m. p. 298—302° (Found: C, 44·0; H, 3·6. Calc. for $C_6H_6ClNO_2$: C, 45·15; H, 3·8. Calc. for $C_6H_6BrNO_2$: C, 35·3; H, 3·0%) had m. p. 302° (from methanol), undepressed on admixture with 2-chloro-4,6-dihydroxy-3-methylpyridine.

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