Polyketo-enols and Chelates. Synthesis of 2-Pyrones, 2-Pyridones, 2-Methoxypyridines, and *m*-Hydroxyanilines by Control of the Cyclisation of Nitrile-substituted Glutaconic Types

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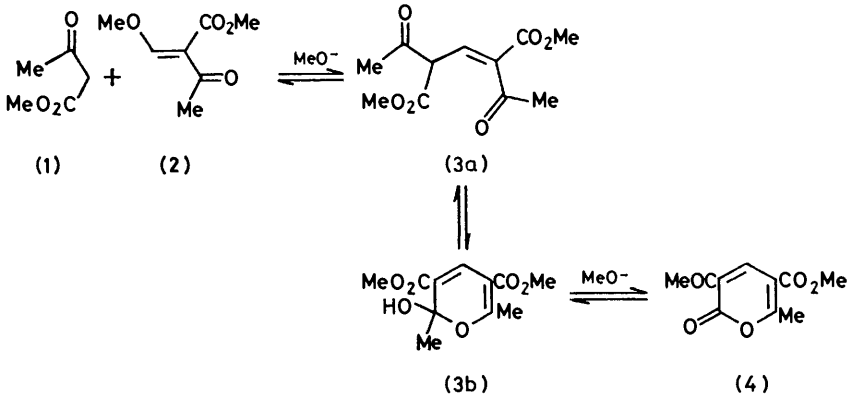
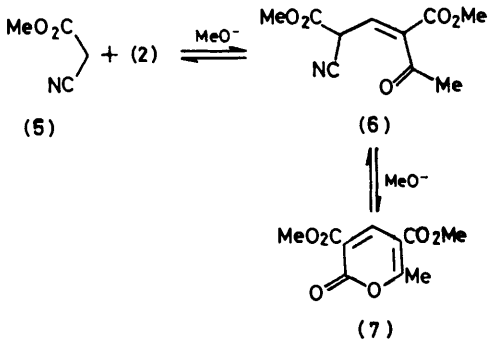
Sodium methoxide-initiated condensation between methyl cyanoacetate and methyl methoxymethyleneacetoacetate leads, *via* a nitrile-substituted propene (glutaconic ester), to a 2-pyridone at low base molarities and to a 2-pyrone at high ones. Employment of high molarities of magnesium methoxide gives, in addition, a *m*-hydroxyaniline. When malononitrile replaces methyl cyanoacetate a 2-methoxypyridine is also formed at high methoxide molarities.

Various examples of these nitrile reactions, which have synthetic potential, are surveyed. Formation of the products (controllable in terms of the nature and molarity of base, nature of substituents, and time and temperature of reaction) can be interpreted as a series of equilibria in which the nitrile-substituted propenes and imino-lactones are central, and the pyridones, alkoxypyridines, and hydroxyanilines are formed irreversibly.

In studies of xanthyrones and glaucyrones we have shown that the formation reaction involves base-catalysed condensation between methyl acetoacetate (1) and methoxymethyleneacetoacetate (2) to give a di-acetylglutaconic ester (3a) [actually existing mainly in cyclic form (3b)]. The latter then undergoes base-catalysed cyclisation to a pyrone (4), and further reactions ensue to give members of the xanthyrone and glaucyrone family.[1] A general investigation of xanthyrones has led us to employ the condensation of nitriles, such as methyl cyanoacetate (5), with methyl methoxymethylene acetoacetate (2) as a method for pyrone synthesis (Scheme 2).[2,3] However, pyridones were also encountered in some condensations and since this synthesis has been little used or studied, the present work was initiated. It emerges that the reaction, generalised in Scheme 3 where Z and Y are electron-withdrawing substituents, can be controlled to form a group of synthetic methods for substituted 2-pyrones (14), 2-pyridones (15), 2-alkoxypyridines (16), and *m*-hydroxyanilines (17). The products from specific reactions show striking dependence on the nature and initial molarity of the base employed, as well as on the nature of Z and Y. Because of the prototropic mobility of the propene flanked by electron withdrawing groups (10), the synthesis can be approached with either component in alkoxymethylated form, *i.e.* (8) + (9) or (12) + (13).



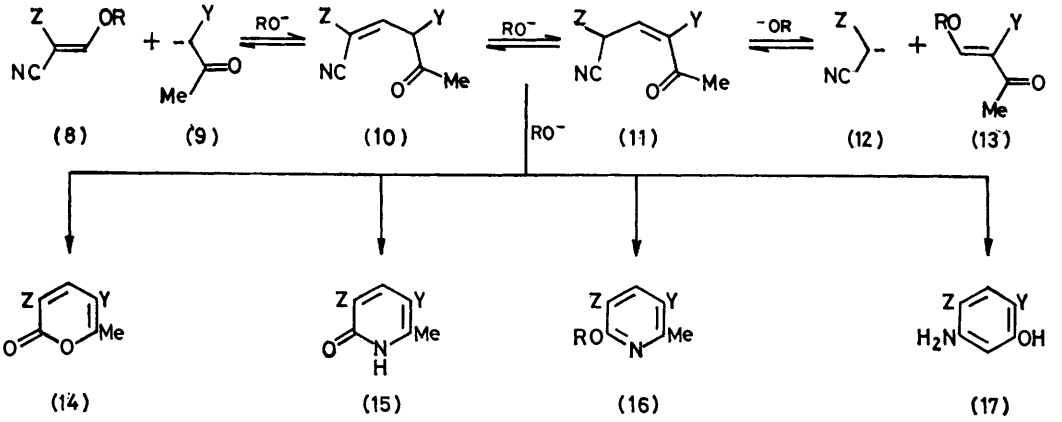
Scheme 1 Formation of 3-acetyl-5-methoxycarbonyl-6-methyl-2-pyrone



Scheme 2 Formation of 3,5-bismethoxycarbonyl-6-methyl-2-pyrone

RESULTS AND DISCUSSION

The first system studied was the sodium methoxide-catalysed condensation between methyl cyanoacetate (5) and methyl methoxymethyleneacetoacetate (2). Table 1 shows that using 0.05 mol of sodium methoxide in refluxing methanol (12 h), a 77% yield of pyridone (22), free from pyrone, can be obtained. On the other hand,



SCHEME 3 Generalised synthetic scheme involving 1-acetyl-3-cyanopropenes

using 4.0 mol of sodium methoxide in refluxing methanol, pyrone (7) could be obtained, free from pyridone, in 67% yield. Low initial molarities of sodium methoxide give predominantly pyridone (22) with lesser amounts of pyrone, and the 1 mol reaction is a turning point. At molarities of $\geqslant$1 mol pyrone (7) is the dominant product.

TABLE 1

Sodium methoxide-catalysed reactions between methyl cyanoacetate (5) (1 mol) and methyl methoxymethyleneacetoacetate (2) (1 mol) in methanol

NaOMe/mol	Reflux time/h	Products (%) Pyridone (22)	Pyrone (7)
0.05	1	28	4
0.05	12	77	0
0.125	1	67	19
0.125	12	79	10
0.5	1	40	17
1.0	1	11	63
2.0	12	0	48
4.0	1	0	67
4.0	12	0	40
1.0	0.25	0	59
0.1	1.0	64	0

In a further experiment, (2), (5), and sodium methoxide were refluxed together in molar proportions for 15 min and the product divided. One half was worked up with hydrochloric acid to give pyrone (7) (59%) and no pyridone. The molarity of methoxide in the second half was adjusted to 0.1M and refluxing was continued for 1 h. Work-up with hydrochloric acid gave pyridone (22) (64%) as the product, with very little pyrone. Separate experiments showed that once formed, the pyridone (7) was stable to refluxing methanolic sodium methoxide (2 mol, 12 h). It may be concluded that, at the point of division an intermediate is present which on normal acid work-up gives pyrone, but which can be altered, when the molarity of the base is lowered, to give pyridone: it is suggested that the intermediate is the iminopyrone (20) and its anion (19).

These observations lead us to postulate Scheme 4. Initially, dimethyl 1-acetyl-3-cyanoglutaconate (6) is formed.[1] With excess of base, the glutaconate ester anion (18) equilibrates with the ionised form of the imino-lactone (19), which is readily hydrolysed by acid to the 2-pyrone (7), the predominant, or sole, product with high molarities of sodium methoxide. At lower molarities of sodium methoxide un-ionised imino-lactone (20) is present in equilibrium with the anion and is susceptible to nucleophilic attack at the 6-position by methoxide ion. The product (21) can recyclise to pyridone, now stable to methoxide attack.

This same reaction between (2) and (5) was next studied as a magnesium methoxide-catalysed reaction and shows a new feature, the formation of the hydroxyaniline (24) (dimethyl 4-hydroxy-6-aminoisophthalate). The results in Table 2 show that low initial base molarity

TABLE 2

Magnesium methoxide-catalysed reactions between methyl cyanoacetate (5) (1 mol) and methyl methoxymethyleneacetoacetate (2) (1 mol) in methanol

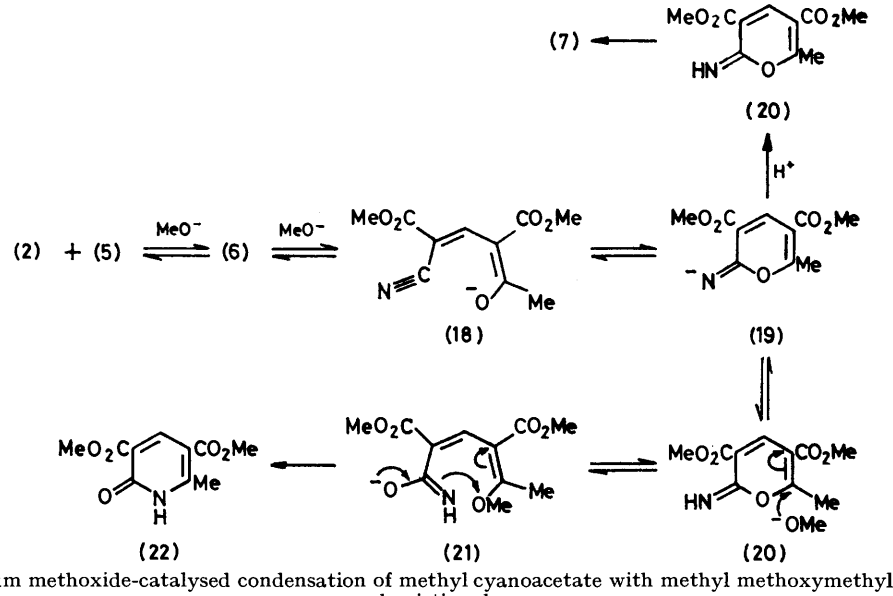
$Mg(OMe)_2$/mol	Reaction time/h (at 20 °C)	Products (%) Pyridone (22)	Pyrone (7)	Aniline (24)
0.125	36	58	21	0
0.5	24	21	45	0
1.0	24	0	52	0
1.0	2 (reflux)	0	41	0
2.0	24	0	50	trace
2.0	2 (reflux)	0	25	25
4.0	24	0	45	39
4.0	72	0	16	69
6.0	24	0	21	59

gives pyridone (22), along with some pyrone, and that near the 1 mol level pyrone (7) can be obtained in about 50% yield. Higher initial base molarities however, or refluxing, or longer reaction time, lead to the formation of increasing amounts of hydroxyaniline (24) with decreasing yields of pyrone. The hydroxyaniline can be obtained in nearly 70% yield.

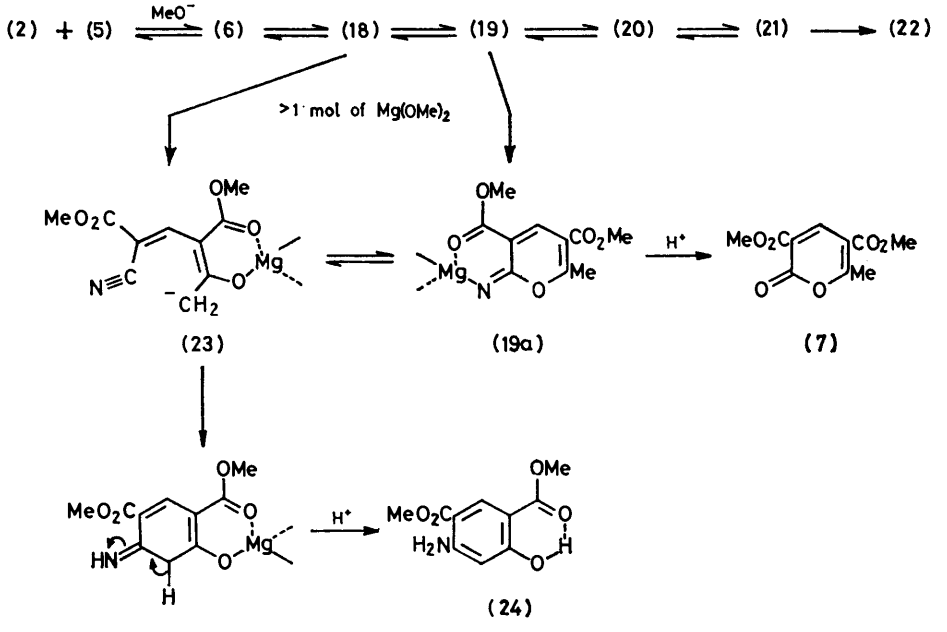
At lower base molarities a mechanistic situation similar to that in Scheme 4 is envisaged, with unchelated and magnesium-chelated compounds being present. However, with large initial molarities of magnesium methoxide, intermediate (18) would be almost entirely present as the metal-chelated form [*cf.* (23)], which is in equilibrium with the imino-chelated form (19a). Work-up of the latter with acid leads to pyrone (7). On the

other hand the chelate (23) can become involved in a further pathway, ultimately irreversible, initiated by formation of the carbon anion (23): such anions are known to form in the presence of excess of magnesium methoxide.[4] Addition to the nitrile, followed by tautomerism, leads to the hydroxyaniline (24). Clearly excess of base, longer reaction time, and higher temperatures, should favour irreversible formation of (24) (held in metal-chelated form until work-up) relative to the pyrone (7), which is held in chelated imino-form (19a), but is presumably able to re-equilibrate with (23). Stabilisation of the intermediate (18), and its carbon anion, as the magnesium chelate (23) is thus an essential feature of the difference between the sodium and magnesium methoxide reactions at high initial base molarities. Formation of a hydroxyaniline in the manner indicated in Scheme 5 presents a highly unusual aniline synthesis from an acyclic precursor, though addition of anions to nitriles is a fairly common step in heterocyclic synthesis.

Table 3 shows the results of a study of the products obtained by treating methyl cyanoacetate (5) and methoxymethyleneacetylacetone (25) with differing initial molarities of sodium methoxide in refluxing



SCHEME 4 Sodium methoxide-catalysed condensation of methyl cyanoacetate with methyl methoxymethyleneacetoacetate: mechanistic scheme



SCHEME 5 Magnesium methoxide-catalysed condensation of methyl cyanoacetate with methyl methoxymethyleneacetoacetate: mechanistic scheme

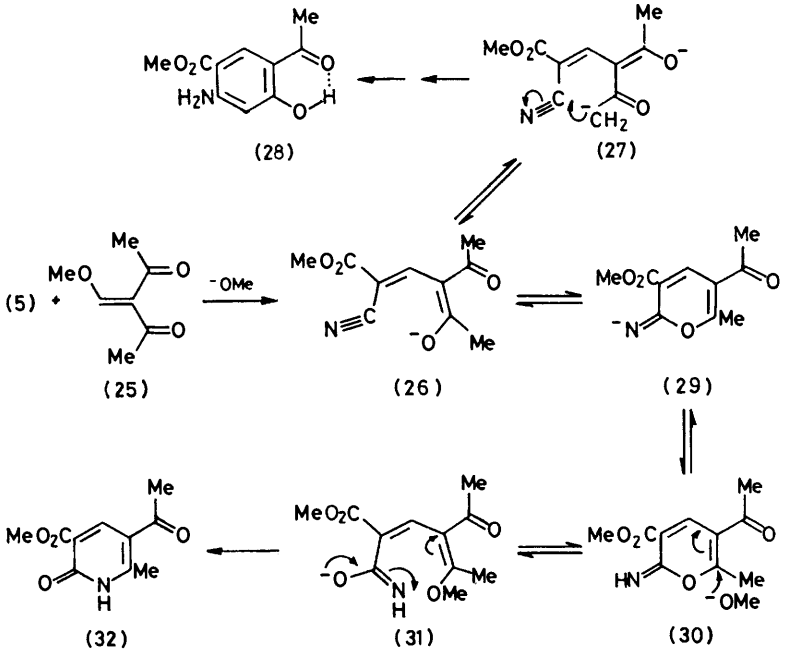
TABLE 3

Sodium methoxide–catalysed reactions between methyl cyanoacetate (5) (1 mol) and methoxymethyleneacetylacetone (25) (1 mol) in methanol

		Products (%)	
NaOMe/mol	Reflux time/h	Pyridone (32)	Aniline (28)
0.125	1	68	0
0.1	12	74	0
1.0	1	41	0
1.0	12	42	0
1.0	12 (20 °C)	38	0
2.0	12 (20 °C)	41	0
2.0	12	0	74
4.0	1	0	60
0.1	1	57	0
2.0	12	60	0

methanol. Lower initial sodium methoxide molarities gave pyridone (32) as before, but under all the conditions used there was no sign of the pyrone; instead, methyl 5-acetyl-4-hydroxyanthranilate (28) was formed in runs using higher initial base molarities. The structure of the hydroxyaniline is consistent with spectral and other data, and for characterisation purposes it was converted, by diazotisation and treatment with ethanol and copper bronze, into the known methyl 3-acetyl-4-hydroxybenzoate. Once formed, the pyridone is stable to methoxide ion as was shown by an experiment which commenced by treatment of (5) and (25) with 0.1 mol magnesium methoxide and refluxing (1 h). Work-up of one half gave pyridone (32) (57%). Adjustment of the sodium methoxide molarity (to 2.0 mol) of the other half followed by refluxing (12 h) gave, again, only pyridone (60%). Formation of pyridone (32) at low base concentrations is envisaged (Scheme 6) as following a similar process to that in Scheme 4. However, the results indicate that the carbon anion (27), with an acetylacetone terminus, forms and cyclises considerably more readily than in the case of the acetoacetate terminus [*i.e.* the carbon anion derived from (18)]. Hence, material otherwise destined to form pyrone *via* its iminoanion [*cf.* (19)] reacts further to give the hydroxyaniline. As might be expected (*cf.* the results of the cyanoacetate–methoxymethyleneacetoacetate experiments), replacement of sodium methoxide by magnesium methoxide does not substantially alter the product situation. Better yields of the hydroxyaniline (28) (87%) are, however, obtained by using 6 mol of magnesium methoxide at 20 °C.

Experiments on the condensation of malononitrile with methyl methoxymethyleneacetoacetate, catalysed by magnesium methoxide at 20 °C, are shown in Table 5 and introduce a new product, the 2-methoxypyridine (39), formed in addition to the pyridone (36) and hydroxyaniline (41). As before, at low magnesium methoxide molarities, the only product is pyridone (36). In runs using 4 mol or more of magnesium methoxide none of the latter was found, the products being methyl 4-amino-3-cyano-6-hydroxybenzoate (41) and methyl 3-cyano-2-methoxy-6-methylpyridine-5-carboxylate (39). Separate experiments showed that the pyridone (36) is not converted into the methoxypyridine (39) by treatment with excess of magnesium methoxide (6 mol), and the production of the three compounds can be accommodated as in Scheme 7. 3-Acetyl-1,1-dicyano-3-methoxycarbonylpropene is formed initially



SCHEME 6 Sodium methoxide-catalysed condensation of methyl cyanoacetate with methoxymethyleneacetylacetone: mechanistic scheme

TABLE 4

Magnesium methoxide-catalysed reactions between methyl cyanoacetate (5) (1 mol) and methoxymethyleneacetylacetone (25) (1 mol) in methanol

$Mg(OMe)_2$/mol	Reaction time/h (20 °C)	Products (%) Pyridone (32)	Aniline (28)
0.125	36	53	0
0.5	24	49	0
1.0	24	34	0
1.5	24	41	11
2.0	24	32	49
2.0	0.5 (reflux)	4	64
2.5	24	0	76
4.0	24	0	83
6.0	24	0	87

TABLE 5

Magnesium methoxide-catalysed reactions between malononitrile (33) (1 mol) and methyl methoxymethyleneacetoacetate (2) (1 mol) in methanol

$Mg(OMe)_2$mol	Reaction time/h (20 °C)	Products (%) Pyridone (36)	Aniline (41)	Pyridine (39)
0.125	24	59	0	0
0.25	24	61	0	0
0.5	24	54	0	0
1.0	24	28	0	0
2.0	24	29	26	20
4.0	24	0	23	26
6.0	24	0	27	41

and, in experiments employing lower molarities of magnesium methoxide, leads to some of the iminolactone (34). Attack on this neutral species by methoxide ion and recyclisation gives the pyridone (36): yields are improved by keeping the initial magnesium methoxide molarity at $\leqslant 0.5$.

In the presence of excess of magnesium methoxide it is expected that the 3-acetyl-1,1-dicyano-3-methoxycarbonylpropene will be held in the complexed form (37). Two routes for further reaction are available. In the first, carbon anion formation leads to the hydroxyaniline. In the second, attack by methoxide ion gives the iminoester anion (38) which cyclises to the 2-methoxypyridine (39). Clearly these two reactions can compete.

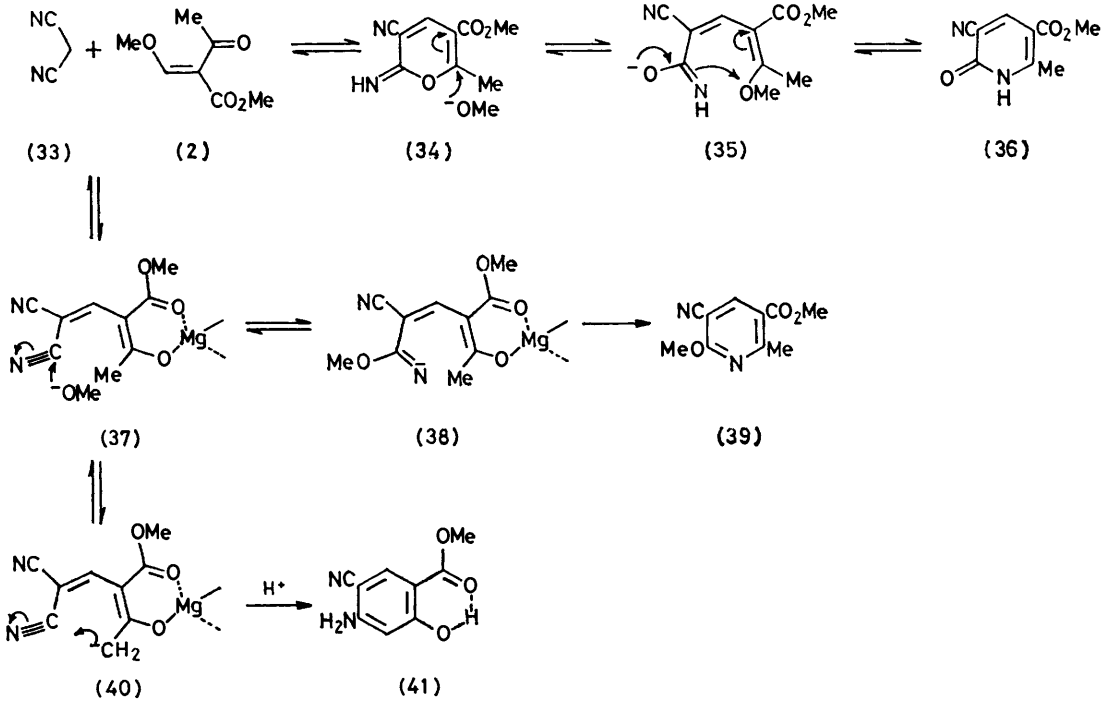
Magnesium methoxide-catalysed reaction between

TABLE 6

Magnesium methoxide-catalysed reactions between malononitrile (33) (1 mol) and methoxymethyleneacetylacetone (25) (1 mol) in methanol

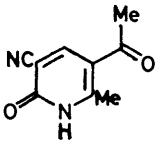
$Mg(OMe)_2$/mol	Reaction time/h (20 °C)	Products (%) Pyridone (42)	Aniline (44)
0.125	24	41	0
0.5	24	16	0
1.0	24	4	26
3.0	24	0	67
6.0	24	0	78

malononitrile (33) and methoxymethyleneacetylacetone (25) produced 5-acetyl-3-cyano-6-methyl-2-pyridone (42) at low magnesium methoxide molarities (0.125—0.5 mol) and 4-amino-5-cyano-2-hydroxyacetophenone (44) at high initial molarities (3—6 mol) (Table 6). The 2-methoxypyridine (43) was not found. The reaction is taken to follow pathways similar to Scheme 7 but in the present case formation and Michael addition of the carbon anion to the nitrile is favoured over external attack by



SCHEME 7 Magnesium methoxide-catalysed condensation of malononitrile and methyl methoxymethyleneacetoacetate: mechanistic scheme

methoxide to initiate the pathway to the 2-methoxypyridine. However, using 2 mol of sodium methoxide in a condensation between acetylacetone and methoxymethylenemalononitrile, 5-acetyl-3-cyano-2-methoxy-6-methylpyridine (43) was isolated (21%) along with lesser amounts of the hydroxyaniline (44). The chelating base appears to favour the step corresponding to (40). Using sodium methoxide apparently disfavours carbon anion formation and addition, allowing attack by external methoxide to become evident. Use of only 1 mol of sodium methoxide in the reaction gave the pyridone (42) (48%).



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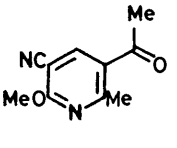

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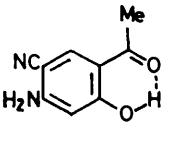

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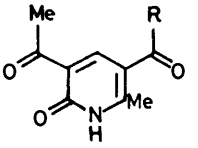
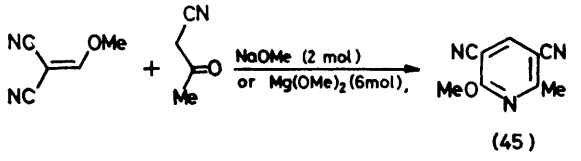


(46)
R = Me
R = OMe

The condensation between cyanoacetone and methoxymethylenemalononitrile was also briefly examined. Catalysis by sodium methoxide (2 mol) or magnesium methoxide (6 mol) led to 3,5-dicyano-2-methoxy-6-methylpyridine (45) (52 and 46% respectively). The chelating base has thus little additional influence here: this seems not surprising as formation of a stable magnesium chelate of the kind which diverts a reaction pathway is not to be expected (Scheme 8). It will be noted however, that methoxypyridine synthesis has been effected only when the parent substituted-propene intermediate has a malononitrile terminus. Imidate-ester formation is favoured by electron-withdrawal in the α-position and the second nitrile group may be particularly effective in this respect.



(45)

SCHEME 8 Formation of 3,5-dicyano-2-methoxy-6-methylpyridine

Two further pyridones (46; R = Me or OMe) were made in sodium methoxide (1 mol) catalysed reactions between cyanoacetone and methoxymethyleneacetylacetone or methyl methoxymethyleneacetoacetate.

The present investigation thus shows, if only in outline, the experimental circumstances which lead to preference for 2-pyrone, 2-pyridone, 2-alkoxypyridine, and *m*-hydroxyaniline formation. Nitrile-substituted propenes and imino-lactones appear to be central to the system of equilibria involved, with 2-pyrones being generated from an imino-lactone by work-up, and 2-pyridones, 2-alkoxypyridines, and *m*-hydroxyanilines being formed by irreversible processes.

EXPERIMENTAL

Unless stated otherwise, u.v. data refer to ethanol solutions, and n.m.r. data are given as τ values.

Reaction of Methyl Methoxymethyleneacetoacetate with Methyl Cyanoacetate catalysed by Sodium Methoxide (0.05 *mol*).—Methyl cyanoacetate (1.55 g) and methyl methoxymethyleneacetoacetate (2.5 g) were added to sodium methoxide [from sodium (0.015 g) and methanol (60 ml)], and the mixture was refluxed for 12 h. The product was cooled, treated with 2N hydrochloric acid, and extracted with chloroform. The extract was washed with water and evaporated to give *3,5-bismethoxycarbonyl-6-methyl-2-pyridone* (22) (2.75 g, 77%), colourless needles from methanol, m.p. 197 °C (Found: C, 53.2; H, 4.7; N, 6.2%, M^+ 225. $C_{10}H_{11}NO_5$ requires C, 53.3; H, 4.9; N, 6.2%); $\nu_{max.}$ (KBr) 3 490 (N–H), 1 740, 1 715 (ester carbonyls), 1 665 (pyridone C=O), and 1 575 cm^{-1}; $\lambda_{max.}$ 206 (ε 19 790), 260 (17 050), and 329 (8 360) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid), no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 209 (ε 37 900), 278 (22 560), and 331 (10 010) nm; τ($CDCl_3$) −3.10(br, 1 H, –NH–), 1.18 (1 H, s, =CH–), 6.10 (6 H, s, 2 × CH_3O), and 7.18 (3 H, s, CH_3). No other product was found.

Reaction of Methyl Cyanoacetate with Methyl Methoxymethyleneacetoacetate catalysed by Sodium Methoxide (2.0 *mol*).—Methyl cyanoacetate (1.55 g) and methyl methoxymethyleneacetoacetate (2.5 g) were added to sodium methoxide [from sodium (0.708 g) and methanol (60 ml)], and the mixture was refluxed for 12 h. Work-up gave 3,5-bismethoxycarbonyl-6-methyl-2-pyrone (7) (1.7 g, 48%), m.p. 90 °C (from methanol) (lit.,[3] m.p. 93 °C), $\nu_{max.}$ 1 765 (pyrone carbonyl), 1 715 (ester carbonyls), and 1 620 cm^{-1}; $\lambda_{max.}$ (ethanol) 248 (ε 9 060) and 320 (8 000) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) 247 (ε 9 380) and 319 (8 040) nm; $\lambda_{max.}$ (ethanolic sodium hydroxide) 265 (ε 14 040) and 342 (23 490) nm; τ($CDCl_3$) 1.32 (1 H, s; =CH–), 6.12 (6 H, s, CH_3O), and 7.27 (3 H, s, CH_3).

Product Analysis for the Methyl Cyanoacetate– and Methyl Methoxymethyleneacetoacetate–Sodium Methoxide Systems (*Table* 1).—Reactions were run using methyl cyanoacetate (1.55 g) and methyl methoxymethyleneacetoacetate (2.5 g) and the appropriate quantity of sodium methoxide in methanol (60 ml). After work-up, an aliquot was removed and dissolved in a standard mixture of $CHCl_3$–$CDCl_3$. Analysis was effected using the chloroform peak at τ 2.72 for reference, the pyridone ring proton at τ 1.18, and the pyrone ring proton at τ 1.32, along with standard mixtures. Results are recorded in Table 1.

Reaction of Methyl Cyanoacetate with Methyl Methoxymethyleneacetoacetate (*Sodium Methoxide Concentration Change from* 1.0 *to* 0.1 *mol*).—Methyl cyanoacetate (3.12 g) was added to sodium methoxide solution [from sodium (0.72 g) and methanol (50 ml)], followed by methyl methoxy-

methyleneacetoacetate (5.0 g). The mixture was refluxed (15 min), cooled, and the solution divided into two equal parts. The first was acidified with 2N hydrochloric acid, and extracted with chloroform. The extract was washed, dried ($MgSO_4$), and evaporated to give 3,5-bismethoxycarbonyl-6-methyl-2-pyrone (7), (2.5 g, 64%).

The second portion was treated with glacial acetic acid so that the quantity of sodium methoxide was reduced from 1.0 to 0.1 mol. The mixture was then refluxed for 1 h. Extraction with chloroform gave 3,5-bismethoxycarbonyl-6-methyl-2-pyridone (22) (2.1 g, 59%). Identities were confirmed by comparison of i.r., n.m.r., and u.v. data.

Reaction of Methyl Cyanoacetate with Methoxymethyleneacetylacetone catalysed by Sodium Methoxide (0.125 *mol*).—Methyl cyanoacetate (1.74 g) was added to sodium methoxide [from sodium (0.05 g) and methanol (30 ml)], followed by methoxymethyleneacetylacetone (2.5 g). The mixture was refluxed for 1 h. After work-up, the solid was crystallised from benzene to give *5-acetyl-3-methoxycarbonyl-6-methyl-2-pyridone* (32) (2.45 g, 68%), m.p. 199 °C (Found: C, 57.3; H, 5.05; N, 6.8%; M^+ 209.068 9. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%; *M* 209.068 8); $\nu_{max.}$ (KBr) 3 480, 1 735 (ester carbonyl), 1 705 (acetyl carbonyl), 1 670 (pyridone carbonyl), and 1 585 cm^{-1}; $\lambda_{max.}$ 274 (ε 12 400) and 327 (7 000) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 228infl. (ε 11 800), 298 (16 800), and 320 (13 100) nm; τ($CDCl_3$) −3.13(br, 1 H, s, NH), 1.25 (1 H, s, =CH−), 6.09 (3 H, s, CH_3O), 7.47 (3 H, s, CH_3CO), and 7.20 (3 H, s; CH_3); τ(CF_3CO_2H), 0.75 (1 H, =CH−), 5.95 (3 H, CH_3O), 6.99 (3 H, CH_3CO), and 7.18 (3 H, CH_3).

Reaction of Methyl Cyanoacetate with Methoxymethyleneacetylacetone catalysed by Sodium Methoxide (2.0 *mol*).—Methyl cyanoacetate (1.74 g) and methoxymethyleneacetylacetone (2.5 g) were added to sodium methoxide solution [from sodium (0.81 g) and methanol (30 ml)], and refluxed (12 h). Work-up and chromatography on neutral alumina eluting with chloroform gave, after crystallisation from chloroform–light petroleum (b.p. 60—80 °C), *methyl 5-acetyl-4-hydroxyanthranilate* (28) (2.6 g, 74%), m.p. 157—159 °C (Found: C, 57.6; H, 5.3; N, 6.3%; M^+ 209. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%); $\nu_{max.}$ (KBr) 3 460, 3 370, 1 675 (ester carbonyl), 1 625 (chelated ketone carbonyl), and 1 565 cm^{-1}; $\lambda_{max.}$ 226infl. (ε 10 060), 245 (31 540), 277 (10 680), 304 (15 690), and 330 (13 620) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 270 (ε 44 250), and 346 (8 650) nm; τ($CDCl_3$) −2.76 (1 H, s, OH, removed by D_2O exchange), 1.68 (1 H, s, aromatic-H), 4.01 (1 H, s, aromatic-H), 4.05 (br, 2 H, NH_2, removed by D_2O exchange), 6.18 (3 H, s, CH_3O), and 7.52 (3 H, s, CH_3CO).

Product Analysis for the Methyl Cyanoacetate– and Methoxymethyleneacetylacetone–Sodium Methoxide System (*Table* 3).—Reactions were run using methyl cyanoacetate (1.74 g) and methoxymethyleneacetylacetone (2.5 g) using the appropriate quantity of sodium methoxide in methanol (60 ml). Analysis was by the n.m.r. method given above using a standard $CHCl_3$–$CDCl_3$ mixture as solvent and the pyridone ring proton at τ 1.25 and the anthranilate proton at τ 1.68, along with standard mixtures. The results are in Table 3.

Reaction of Methyl Cyanoacetate with Methoxymethyleneacetylacetone (*Sodium Methoxide Concentration Change from* 0.1 *to* 2.0 *mol*).—Methyl cyanoacetate (3.48 g) was added to sodium methoxide [from sodium (0.08 g) and methanol (60 ml)], followed by methoxymethyleneacetylacetone (5.0 g), and the mixture was refluxed for 1 h. The solution was cooled, and divided into two equal parts.

Chloroform was added to one part, and the extracted solid was crystallised from benzene to give 5-acetyl-3-methoxycarbonyl-6-methyl-2-pyridone (32) (2.1 g, 57%), characterised by i.r. and n.m.r. data.

The second part of the solution was treated with sodium methoxide solution so that the quantity of sodium methoxide was changed from 0.1 to 2.0 mol. During the addition of the sodium methoxide a precipitate formed, apparently the sodio-pyridone. The mixture was refluxed for 12 h, cooled, and worked up to give the pyridone (32), (2.2 g, 60%), characterised as above.

Methyl 3-Acetyl-4-hydroxybenzoate.—To a cold mixture of 95% ethanol (35 ml), and concentrated sulphuric acid (16 ml) was added methyl 5-acetyl-4-hydroxyanthranilate (28) (11.4 g). The mixture was stirred, cooled to 10 °C, and a solution of sodium nitrite (6.1 g) in water (11 ml) added, the temperature being maintained below 10 °C. After stirring (20 min), copper bronze (1.43 g) was added, and after 5 min, the mixture was warmed on a water-bath (10 min). Extraction ($CHCl_3$) and chromatography on neutral alumina, eluting with chloroform, gave methyl 3-acetyl-4-hydroxybenzoate (3.85 g, 37%), needles from cyclohexane, m.p. 96 °C (lit.,[5] m.p. 98 °C) (Found: C, 62.6; H, 5.2%; M^+ 194. $C_{10}H_{10}O_4$ requires C, 61.9; H, 5.2%); $\nu_{max.}$ (KBr) 1 715 (ester carbonyl), and 1 640 (chelated acetyl carbonyl) cm^{-1}; $\lambda_{max.}$ 231 (ε 32 100), 254 (9 840), and 321 (2 820) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 227infl. (ε 10 200), 245 (18 500), 296 (23 400), and 357 (6 240) nm; τ($CDCl_3$) −2.58 (1 H, s; OH removed by D_2O exchange), 1.61 (1 H, d, aromatic-H, *J* 2 Hz), 1.84 (1 H, dd, aromatic-H, *J* 9 and 2 Hz), 2.99 (1 H, d, aromatic-H; *J* 9 Hz), 6.11 (3 H, s, CH_3O), and 7.33 (3 H, s, CH_3CO).

Reaction of Methyl 3-Acetyl-4-hydroxybenzoate with Potassium Hypobromite.—Potassium hypobromite [from bromine (2.5 g) and potassium hydroxide (2.6 g) in water (10 ml) at 3—7 °C] was added to the hydroxybenzoate (1.0 g) in dioxan (23 ml), and stirred for 1 h. It was refluxed with stirring (1 h), cooled, and sodium bisulphite (0.2 g) added followed by 8% potassium hydroxide solution (5 ml). The mixture was extracted with ether, and concentrated hydrochloric acid was added to precipitate a white solid, which, recrystallised from aqueous methanol, gave *3-acetyl-5-bromo-4-hydroxybenzoic acid* (0.85 g, 64%), m.p. 243 °C (Found: C, 42.1; H, 3.0; Br, 31.9%; M^+ 259. $C_9H_7BrO_4$ requires C, 41.9; H, 2.7; Br, 31.0%); $\nu_{max.}$ (KBr) 1 684 (acid carbonyl), 1 645 (acetyl carbonyl), and 1 600 cm^{-1}; $\lambda_{max.}$ 234 (28 480), 258infl. (9 130), and 330 (3 160) nm; $\lambda_{max.}$ (ethanolic sodium hydroxide) 251 (ε 21 680), 283 (13 300), and 372 (6 070) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) 234 (ε 29 380), 256infl. (9 500), and 330 (3 260) nm; τ[$(CD_3)_2SO$] −3.2(br, 1 H, OH), 1.56 (1 H, d, aromatic-H, *J* 2 Hz), 1.72 (1 H, d, aromatic-H, *J* 2 Hz), and 7.26 (3 H, s, CH_3CO).

Reaction of Methyl Cyanoacetate with Methyl Methoxymethyleneacetoacetate catalysed by Magnesium Methoxide (6.0 mol).—Methyl cyanoacetate (1.56 g) and methyl methoxymethyleneacetoacetate (2.5 g) were added to magnesium methoxide solution [from magnesium (2.36 g) and methanol (100 ml)]. The temperature was kept below 10 °C during the addition, and the mixture was stirred at room temperature for 24 h. Chloroform was added, then

2N aqueous hydrochloric acid. The chloroform layer was separated and the extract isolated and separated into oily and crystalline material. The latter was chromatographed on alumina, eluting with chloroform, and crystallised from cyclohexane–chloroform to give dimethyl 4-hydroxy-6-aminoisophthalate (24) (2.1 g, 59%), m.p. 144 °C (lit.,[6] m.p. 144—145 °C) (Found: C, 53.5; H, 4.9; N, 5.9%; M^+ 225. $C_{10}H_{11}NO_5$ requires C, 53.3; H, 4.9; N, 6.2%); $\nu_{max.}$ (KBr) 3 510, 3 400, 1 705 (ester carbonyl), 1 660 (chelated ester carbonyl), and 1 640 cm^{-1}; $\lambda_{max.}$ 241 (ε 41 200), 261 (12 140), 288 (18 120), and 320 (12 570) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 260 (ε 53 100), 278infl. (21 520), and 322 (8 050) nm; τ($CDCl_3$) −1.02 (1 H, s, OH, removed by D_2O exchange), 1.62 (1 H, s, aromatic-H), 3.9 (br, 2 H, s, NH_2, removed by D_2O exchange), 3.96 (1 H, s, aromatic-H), 6.17 (3 H, s, CH_3O), and 6.22 (3 H, s, CH_3O).

A little methanol was added to the oily material (above), and the mixture was set aside at 0 °C. 3,5-Bismethoxycarbonyl-6-methyl-2-pyrone (7) was isolated (0.75 g, 21%).

Product Analysis for the Methyl Cyanoacetate– and Methyl Methoxymethyleneacetoacetate–Magnesium Methoxide Systems (*Table* 2).—Reactions were run using methyl cyanoacetate (1.56 g) and methyl methoxymethyleneacetoacetate (2.5 g) and the appropriate quantity of magnesium methoxide in methanol (100 ml). The mixture was then stirred for the appropriate time. After acidification, chloroform extraction, and work-up the product was dissolved in a standard $CHCl_3$–$CDCl_3$ mixture and analysed by n.m.r., using for the pyrone (7) the resonance at τ 1.22, for the pyridone (22) that at τ 1.18, and for the hydroxyaniline (24) that at τ 1.62.

Product Analysis for the Methyl Cyanoacetate– and Methoxymethyleneacetylacetone–Magnesium Methoxide Systems (*Table* 4).—Reactions were run using methyl cyanoacetate (1.74 g) and methoxymethyleneacetylacetone (2.5 g) and the appropriate quantity of magnesium methoxide in methanol (100 ml). Analyses (see above) were by n.m.r., using the resonance at τ 1.25 for 5-acetyl-3-methoxycarbonyl-6-methyl-2-pyridone (32) and τ 1.68 for 5-acetyl-4-hydroxyanthranilate (28).

Reaction of Malonitrile and Methyl Methoxymethyleneacetoacetate catalysed by Magnesium Methoxide (6.0 *mol*).—Malononitrile (2.3 g) and methyl methoxymethyleneacetoacetate (5.5 g) were added to magnesium methoxide [from magnesium (6.125 g) and methanol (100 ml)], the temperature being kept below 5 °C. The mixture was set aside at room temperature for 24 h, the methanol was removed under reduced pressure, and the residue treated with 4N hydrochloric acid. Filtration and crystallisation from methanol gave *methyl 4-amino-3-cyano-6-hydroxybenzoate* (41), needles (2.3 g, 33%), m.p. 208—209 °C (Found: C, 56.15; H, 4.30; N, 14.36%; M^+ 192. $C_9H_8N_2O_3$ requires C, 56.25; H, 4.20; N, 14.58%); $\nu_{max.}$ (KBr) 2 220 (nitrile), 1 675 (chelated ester carbonyl), 1 640, 1 620, and 1 580 cm^{-1}; $\lambda_{max.}$ 234 (ε 46 100), 257 (11 690), 285 (18 220), and 318 (6 730) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 251 (ε 55 850), 273 (15 580), and 330 (6 820) nm; τ[$(CD_3)_2SO$] −0.95 (1 H, s, OH), 2.12 (1 H, s, aromatic-H), 3.22 (2 H, s, NH_2), 3.78 (1 H, s, aromatic-H), and 6.16 (3 H, s, CH_3O).

Evaporation of the mother liquors from the crystallisation gave a solid, recrystallised from cyclohexane as needles of *methyl 5-cyano-6-methoxy-2-methylpyridine-3-carboxylate* (39) (3.1 g, 43%), m.p. 143—144 °C (Found: C, 58.45; H, 4.60; N, 13.2%; M^+ 206. $C_{10}H_{10}N_2O_3$ requires C, 58.3; H, 4.85; N, 13.6%); $\nu_{max.}$ (KBr) 2 230 (nitrile), 1 715 (ester carbonyl), 1 595, and 1 555 cm^{-1}; $\lambda_{max.}$ 210 (ε 32 020), 212 (32 400), 250 (12 850), 290 (7 480), and 294 (7 260) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) and $\lambda_{max.}$ (ethanolic sodium hydroxide) showed no change; τ[$(CD_3)_2SO$] 1.45 (1 H, s, aromatic-H), 5.94 (3 H, s, CH_3O), 6.18 (3 H, s, CH_3O), and 7.28 (3 H, s, CH_3); τ($CDCl_3$) 1.60, 5.92, 6.11, and 7.20.

Product Analysis for the Methyl Methoxymethyleneacetoacetate–Malononitrile–Magnesium Methoxide System (*Table* 5).—Malononitrile (330 mg) and methyl methoxymethyleneacetoacetate (790 mg) were added to the appropriate quantity of magnesium methoxide in methanol (20 ml) and treated as indicated in the Table. On work-up the product was chromatographed on silica gel HF_{254} plates (20 × 40 cm) eluting with chloroform and methanol (150 : 1). The more polar product was methyl 4-amino-3-cyano-6-hydroxybenzoate (41) and the less polar methyl 5-cyano-6-methoxy-2-methylpyridine-3-carboxylate (39): these were eluted, weighed, and their identities checked.

In the experiment using 2.0 mol of magnesium methoxide the third, and most polar compound was isolated as *3-cyano-5-methoxycarbonyl-6-methyl-2-pyridone* (36), prisms from methanol, m.p. 275—277 °C (Found: C, 55.9; H, 4.3; N, 14.6%; M^+ 192. $C_9H_8N_2O_3$ requires C, 56.2; H, 4.2; N, 14.6%); $\lambda_{max.}$ (ethanol) 208 (ε 16 600), 215(sh) (13 800), 261 (15 490), and 331 (9 550) nm; $\nu_{max.}$ (KBr) 3 490, 3 200—2 700 (NH), 2 260 (CN), 1 710 (ester), and 1 660 (pyridone, CO) cm^{-1}; τ($CDCl_3$ + trifluoroacetic acid) 1.30 (s, 1 H), 6.05 (s, 3 H), and 7.18 (s, 3 H).

Reaction of Malononitrile and Methoxymethyleneacetylacetone catalysed by Magnesium Methoxide (6.0 mol).—Malononitrile (2.3 g) and methoxymethyleneacetylacetone (5.0 g) were added to magnesium methoxide [from magnesium (5.125 g) and methanol (100 ml)], at <5 °C. The mixture was set aside at 20 °C for 24 h. Excess of 2N hydrochloric acid was added, and the precipitate was filtered and crystallised from methanol to give *4-amino-2-hydroxy-5-cyanoacetophenone* (44) (4.5 g, 89%), needles, m.p. 243 °C (decomp.) (Found: C, 61.5; H, 4.65; N, 15.9%; M^+ 176. $C_9H_8N_2O_2$ requires C, 61.35; H, 4.60; N, 15.9%); $\nu_{max.}$ (KBr) 3 470, 3 390, 2 230 (nitrile), 1 640 (chelated acetyl carbonyl), and 1 570 cm^{-1}; $\lambda_{max.}$ 233infl. (ε 28 790), 239 (35 340), 271 (8 810), 300 (15 300), and 328 (12 670) nm; $\lambda_{max.}$ (ethanolic hydrochloric acid) no change; $\lambda_{max.}$ (ethanolic sodium hydroxide) 259 (49 000), 280infl. (17 140), and 350 (7 850) nm; τ[$(CD_3)_2SO$] −2.81 (1 H, s, OH), 1.85 (1 H, s, aromatic-H), 3.08 (2 H, s; NH_2), 3.86 (1 H, s, aromatic-H), and 7.51 (1 H s, CH_3CO).

Product Analysis for the Methoxymethyleneacetylacetone–Malononitrile–Magnesium Methoxide System (*Table* 6).—Malononitrile (330 mg) and methoxymethyleneacetylacetone (710 mg) were added to the appropriate quantity of magnesium methoxide in methanol (20 ml) and treated as indicated in the Table. On work-up the product was chromatographed on silica gel HF_{254} plates, eluting with chloroform and methanol (150 : 1), and yields were estimated by weighing. *5-Acetyl-3-cyano-6-methyl-2-pyridone* (42), isolated from the 0.125 mol magnesium methoxide experiment, crystallised from methanol, m.p. 226—227 °C (Found: C, 61.05; H, 4.7; N, 15.65%; M^+ 176. $C_9H_8N_2O_2$ requires C, 61.35; H, 4.60; N, 15.9%); $\lambda_{max.}$ 213 (ε 17 100), 218 (14 000), 274 (14 850), and 334 (9 250) nm; $\nu_{max.}$ 3 400 (NH), 2 220 (CN), 1 680 (acyl CO), and 1 660

(pyridone CO) cm^{-1}; τ[$(CD_3)_2SO$] 1.36 (s, 1 H), 7.43 (s, 3 H), and 7.54 (s, 3 H).

3,5-*Dicyano*-2-*methoxy*-6-*methylpyridine* (45).—Cyanoacetone (0.41 g), methoxymethylenemalononitrile (0.54 g), and sodium methoxide [from sodium (0.23 g) and methanol (25 ml)] were refluxed for 3 h. Work-up and crystallisation from toluene, and then methanol, gave 3,5-*dicyano*-2-*methoxy*-6-*methylpyridine* (45) (0.45 g, 52%), needles, m.p. 201—202 °C (Found: C, 61.95; H, 4.0; N, 24.05. $C_9H_7N_3O$ requires C, 62.4; H, 4.05; N, 24.3%); $\nu_{max.}$ (KBr) 2 250 cm^{-1}; $\lambda_{max.}$ 222 (ε 37 500), 280 (25 700), and 333 (14 400) nm, τ($CDCl_3$) 1.98 (1 H, s), 5.89 (3 H, s), and 7.25 (3 H, s).

Using magnesium methoxide as the base [from magnesium (0.73 g) in methanol (35 ml)], 3,5-dicyano-2-methoxy-6-methylpyridine (45) (0.4 g, 46%), m.p. 201—303 °C, was obtained.

5-*Acetyl*-3-*cyano*-6-*methyl*-2-*pyridone* (42).—Acetylacetone (0.50 g) was added to sodium methoxide [from sodium (0.115 g) and methanol (20 ml)]. Methoxymethylenemalonitrile (0.54 g) was added and stirred for 15 min at room temperature. Work-up and crystallisation from methanol gave 5-*acetyl*-3-*cyano*-6-*methyl*-2-*pyridone* (42) (0.42 g, 48%), needles, m.p. 232 °C (decomp.) (Found: C, 61.00; H, 5.2; N, 15.4%; M^+ 176. $C_9H_8N_2O_2$ requires C, 61.35; H, 4.60; N, 15.9%), $\lambda_{max.}$ (trifluoroacetic acid) 267 (13 300) and 309 (13 000) nm, τ(CF_3CO_2D) 0.75 (1 H, s), 7.10 (3 H, s), and 7.16 (3 H, s).

5-*Acetyl*-3-*cyano*-2-*methoxy*-6-*methylpyridine* (43).—Acetylacetone (0.50 g), methoxymethylenemalononitrile (0.54 g), and sodium methoxide [from sodium (0.23 g) and methanol (20 ml)], were refluxed for 3 h. Work-up and crystallisation from cyclohexane gave 5-*acetyl*-3-*cyano*-2-*methoxy*-6-*methylpyridine* (43) (0.2 g, 21%), m.p. 135—136 °C (Found: C, 63.2; H, 5.45; N, 14.8. $C_{10}H_{10}N_2O_2$ requires: C, 63.15; H, 5.25; N, 14.75%); $\nu_{max.}$ (KBr) 2 250, 1 690, 1 597, 1 551, and 1 485 cm^{-1}; $\lambda_{max.}$ 220 (ε 32 800), 241infl. (9 700), 259 (14 600), and 294 (11 500) nm, τ($CDCl_3$) 1.85 (1 H, s), 5.92 (3 H, s), 7.25 (3 H, s), and 7.45 (3 H, s).

Evaporation of mother liquors gave 4-amino-2-hydroxy-5-cyanoacetophenone (44), m.p. and mixed m.p. 230—231 °C, and t.l.c. and n.m.r. comparison.

* Experiments by M. Eskins.

*Sodium Methoxide–catalysed Condensation of Cyanoacetone with Methyl Methoxymethyleneacetoacetate and with Methoxymethyleneacetylacetone.**—Cyanoacetone (9.9 g) was added to cooled sodium (2.3 g) in methanol (50 ml), followed by methyl methoxymethyleneacetoacetate (15.8 g). Work-up gave 3-*acetyl*-5-*methoxycarbonyl*-6-*methyl*-2-*pyridone* (46; R = OMe) (5.5 g), m.p. 260 °C (decomp.) (Found: C, 57.6; H, 5.25%; M^+ 209.068 9. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3%; M^+ 209.068 8); $\nu_{max.}$ (mull) 1 724 (ester CO), 1 692 (acetyl CO), 1 664 (pyridone CO), and 1 584 cm^{-1}; $\lambda_{max.}$ (neutral and acid ethanol) 264 (ε 15 300) and 340 (8 900) nm; $\lambda_{max.}$ (ethanolic potassium hydroxide) 234infl. (ε 15 100), 282 (23 800), and 348 (16 300) nm; τ(CF_3CO_2H) 0.56 (1 H, –CH=), 5.88 (3 H, CH_3O), 6.89 (3 H, CH_3CO), and 7.09 (3 H, CH_3).

Cyanoacetone (4.2 g) was added to cooled sodium (1.2 g) in methanol (50 ml), followed by methoxymethyleneacetylacetone (7.5 g). Work-up gave 3,5-*diacetyl*-6-*methyl*-2-*pyridone* (46; R = Me) (7.7 g), m.p. 255 °C (decomp.) from chloroform (Found: C, 62.85; H, 5.75; N, 7.35%; M^+ 193.074 9. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.75; N, 7.25%; M^+ 193.073 9); $\nu_{max.}$ ($CHCl_3$) 1 691 (acetyl CO), 1 660 (pyridone CO), and 1 572 cm^{-1}; $\nu_{max.}$ (mull) 1 695, 1 673, and 1 572 cm^{-1}; $\lambda_{max.}$ (neutral and acid ethanol) 278 (ε 16 300) and 345 (10 000), $\lambda_{max.}$ (ethanolic potassium hydroxide) 237infl. (ε 12 300), 298 (ε 22 000), and 348 (12 000) nm; τ(CF_3CO_2H) 0.64 (1 H, –CH=), 6.92 (6 H, 2 × CH_3CO), and 7.11 (3 H, CH_3).

We thank the S.R.C. (D. A. S.), the University of Nottingham (S. R. B.), and Shell Research (R. V. D.) for studentships.

[8/321 *Received*, 23*rd February*, 1978]

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