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THE KNOEVENAGEL REACTION OF MALONONITRILE WITH SOME CYCLIC β-KETO-ESTERS—II[1]

MECHANISM OF FORMATION OF HETEROCYCLIC REACTION PRODUCTS[2]

J. L. VAN DER BAAN and F. BICKELHAUPT*

Scheikundig Laboratorium der Vrije Universiteit, De Lairessestraat 174, Amsterdam, The Netherlands

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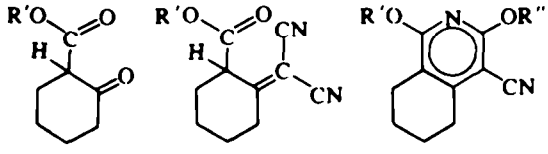
Abstract—The formation of alkoxypyridinols **3a** and **3b** from the Knoevenagel reaction products **2a** and **2b** was shown to proceed by a mechanism in which the ester CO group initiates ring closure by intramolecular nucleophilic attack on the cyano group, possibly assisted by an acidic catalyst. Opening of the oxygen ring after nucleophilic attack by a basic catalyst on the former ester carbonyl C atom results in the formation of an amide, which in turn affords the alkoxypyridinols by a conventional cyclization mechanism.

INTRODUCTION

The Knoevenagel reaction of 1,3-dicarbonyl compounds with malonic acid derivatives is one of the most customary and useful methods for the synthesis of 2-pyridinols and 2,6-pyridinediols.† The formation of 2-pyridinols is usually accomplished by the condensation of 1,3-diketones with cyanoacetamide, cyanoacetic acid esters or malononitrile, while 2,6-pyridinediols have been obtained mostly from the reaction of β-keto-esters and cyanoacetamide. Normal Knoevenagel condensation products are generally assumed as intermediates in these reactions.[1]

Strikingly, in the reaction of β-keto-esters and cyanoacetic acid esters no heterocyclic reaction products have been reported so far: the reaction stops with the formation of the normal Knoevenagel reaction product.[4] To our knowledge, a similar reaction of a β-keto-ester with malononitrile was mentioned only once in the literature and most probably furnished also only the normal Knoevenagel reaction product.[5]

Some time ago we investigated the Knoevenagel reaction of some cyclic β-keto-esters with malononitrile. Under certain conditions (boiling benzene/alcohol solution with ammonium acetate/acetic acid as a catalyst) the reaction took an unexpected course and alkoxypyridinols were formed via the (isolable) normal condensation products,[1] e.g. **1a** → **2a** → **3a** and **1b** → **2b** → **3b** (Scheme 1).



1
a: R' = Me
b: R' = Et
c: R' = t-Butyl

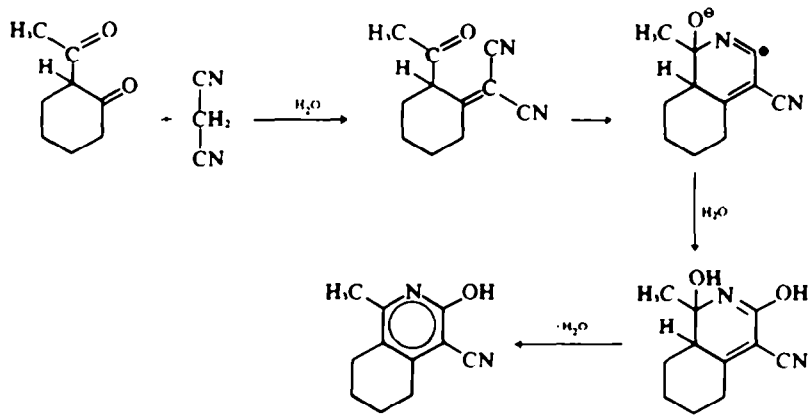
2
a: R' = Me
b: R' = Et
c: R' = t-Butyl

3
a: R' = Me; R'' = H
b: R' = Et; R'' = H
c: R' = H; R'' = H
d: R' = Et; R'' = Et
e: R' = H; R'' = Et

SCHEME 1.

Whereas the mechanism of the first step (Scheme 1, e.g. **1a,b** → **2a,b**) in similar cases has been the subject of extensive investigations,[6] the literature gave no indication for a satisfactory cyclization mechanism (Scheme 1, e.g. **2a,b** → **3a,b**). A mechanism analogous to that of Brody *et al.*[1a] and of Freeman[7] for the reaction of 1,3-diketones with malononitrile in ethanol (Scheme 2) is not applicable to the conversion of **2b** into **3b** or analogous reactions, for in that case one would expect to obtain pyridine derivatives such as **3d** or **3e** by reaction of the very reactive intermediate nitrilium ion with excess ethanol, rather than the alkoxypyridinol **3b**, which is in fact the only product observed.

†The term pyridinol or pyridinediol is used without reference to the actual position of the pyridinol-pyridone equilibrium.



SCHEME 2.

The scarce information available concerning the conversion of Knoevenagel reaction products to pyridine derivatives and the unprecedented retention of the alkoxy group in the cyclization step lead us to a detailed investigation into the mechanism of formation of the heterocyclic products **3a,b** from **2a,b**.

RESULTS AND DISCUSSION

Catalytic effects. Since the investigations of Cope[8] the combination of ammonium acetate and acetic acid has been used frequently as a catalyst in Knoevenagel reactions.[6] As it was not certain whether Cope's catalyst or its components had also a catalytic effect on the cyclization reaction, the degree of conversion of **2b** in boiling dry ethanol, with and without addition of the components of the catalyst, was determined after 24 h reaction time. When NH_4OAc and HOAc were added as usual, a 84% yield of **3b** was obtained. The reaction was retarded by a factor 5·5 (16% yield) when both components were omitted, whilst the presence of only HOAc (35% yield) or NH_4OAc (55% yield) in the reaction mixture was less effective than the combination of both.

To avoid complicating factors, in the following experiments neither HOAc nor NH_4OAc was added. However, after evaluation of the results obtained from the uncatalyzed reaction, the function of the combined catalysts NH_4OAc/HOAc could be elucidated.

Reaction of methyl 2-dicyanomethylenecyclohexanecarboxylate (**2a**) *in ethanol*

A detailed picture of the "uncatalyzed" reaction was obtained by studying the conversion of *methyl* ester **2a** in boiling dry *ethanol*. The reaction was monitored during 96 h by withdrawing aliquots from the reaction mixture and determining the amounts of starting material **2a**, ethyl ester **2b** and the cyclization products **3a** and **3b** (Experimental). The results are presented in Table 1 and Fig 1.

Table 1. Reaction of **2a** in boiling ethanol

Reaction time in h	Percent of conversion to (**3a** + **3b**)	**2b** in % of (**2a** + **2b**)	**3b** in % of (**3a** + **3b**)
2	1		
4	2		
8	4·5	ca. 4	49
14	8	ca. 8	51·5
20	12	19	55
24	15	27	57·5
27	17·5		
32	23	45	65
36	28	57	71
48	44	84	79
56	54	91	
60	58		
72	69	97	88
84	78		
90	81		
96	83	98	89

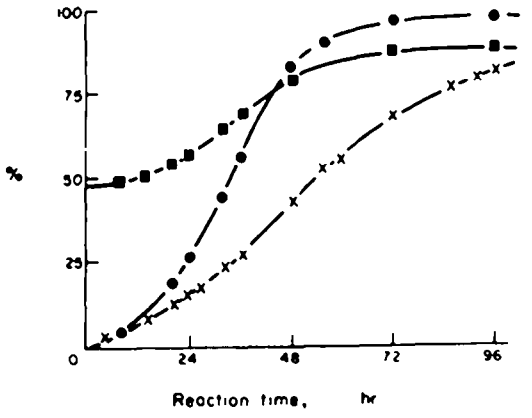
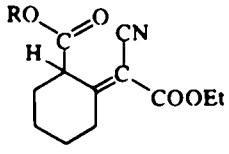
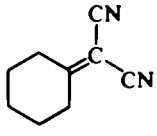


Fig 1. Reaction of **2a** in boiling ethanol. ×: % of conversion to (**3a** + **3b**); ●: **2b** in % of (**2a** + **2b**); ■: **3b** in % of (**3a** + **3b**).

First of all it is evident from the S-shaped curves in Fig 1, that the rate of both the cyclization and the transesterification is affected by the formation of the (weakly) acidic pyridinols, which is in accordance with the established catalytic effect of acetic acid. Secondly it is seen that the transesterification (**2a** → **2b**) is faster than the cyclization; as a consequence **3b** is the main product in the final reaction mixture. A third important conclusion can be derived from the relation between reaction time and the ratio **3b**:(**3a** + **3b**). When the reaction starts, i.e. at a time when transesterification is hardly of any importance, the ratio of **3a**:**3b** is close to 1:1. As **3a** is not converted to **3b** under these conditions, this implies that in this reaction ethoxypyridinol **3b** originates not only via transesterification of **2a** to **2b**, but also directly from methyl ester **2a**. It follows that one of the intermediates in the cyclization reaction, presumably formed by nucleophilic attack of ethanol on the methoxy-bearing (former) ester CO group, must contain the two different alkoxy groups in equivalent positions, so that in a later stage one of them is expelled (irreversibly) with (almost) equal probability.



4



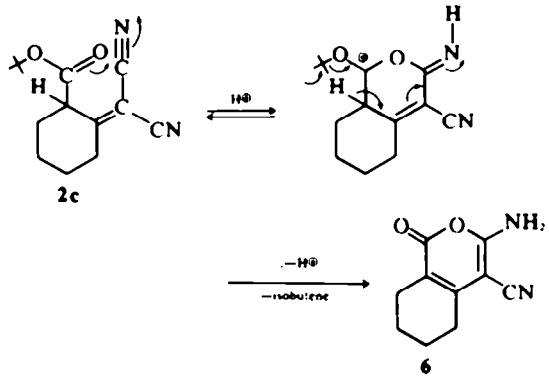
5

a: R = Me
b: R = t-Butyl

Because **4a**, which is closely related to **2a**, does not show the slightest tendency to exchange its methoxy group in boiling ethanol (nor in the presence of NH_4OAc and/or HOAc), a neighbouring group effect of the dicyanomethylene function must be responsible for the fast transesterification of **2a** (the same applies to **2b** in boiling methanol) in comparison to **4a**. As also no trace of a heterocyclic reaction product could be detected when **4a** was subjected to the usual cyclization conditions, a close relationship between ring closure and transesterification, i.e. the possibility of a reaction via a common intermediate, became apparent.

Reaction of t-butyl 2-dicyanomethylenecyclohexanecarboxylate (**2c**) *in ethanol*

In contrast to the corresponding methyl and ethyl esters **2a** and **2b**, respectively, the reaction of t-butyl ester **2c** in boiling dry ethanol did not yield a pyridinol, but a compound without a t-butyl group, to which on the basis of spectral data, elemental analysis and reactivity[2,9] the structure of 3 - amino - 4 - cyano - 5,6,7,8 - tetrahydroisocoumarin (**6**) was assigned.



2c **6**

SCHEME 3.

This reaction can be envisaged to proceed by a mechanism in which the ester CO group, probably assisted by an acidic catalyst,* initiates ring closure by nucleophilic attack on one of the cyano groups, followed by elimination of isobutene from the positive intermediate (Scheme 3). A mechanism involving elimination of isobutene before ring closure (i.e. the "normal" acid catalyzed elimination of isobutene from t-butyl esters[10]) is unlikely because the intermediate carboxylic acid would be expected to lose carbon dioxide very rapidly in refluxing ethanol, whereas not even a trace of the resulting decarboxylation product **5** was found.†

Furthermore, and in analogy with the differing behaviour of **4a**, t-butyl ester **4b** was unaffected by boiling in ethanol, even in the presence of acetic acid. Obviously, for both the transesterification and the cyclization/elimination reaction, the presence of the second cyano group is necessary. As Itoh *et al.*[4a] have shown **4a** to consist of an approximately 1:1 mixture of the two double bond isomers, an anti-relation of the carbomethoxy- and the cyano group (geometric isomer of formula **4a**) cannot be the reason for its lack of reactivity. The same holds true for **4b**; two peaks for the t-butyl group of about equal intensity at $\delta = 1{\cdot}51$ and $1{\cdot}53$ indicate the presence of the two geometric isomers. We therefore feel that the activating influence of the second cyano group is electronic of origin; presumably it makes the C atom of the first cyano group more susceptible to nucleophilic attack than does the second ester group in **4**.

Reaction of methyl 2-dicyanomethylenecyclohexanecarboxylate (**2a**) *in water*

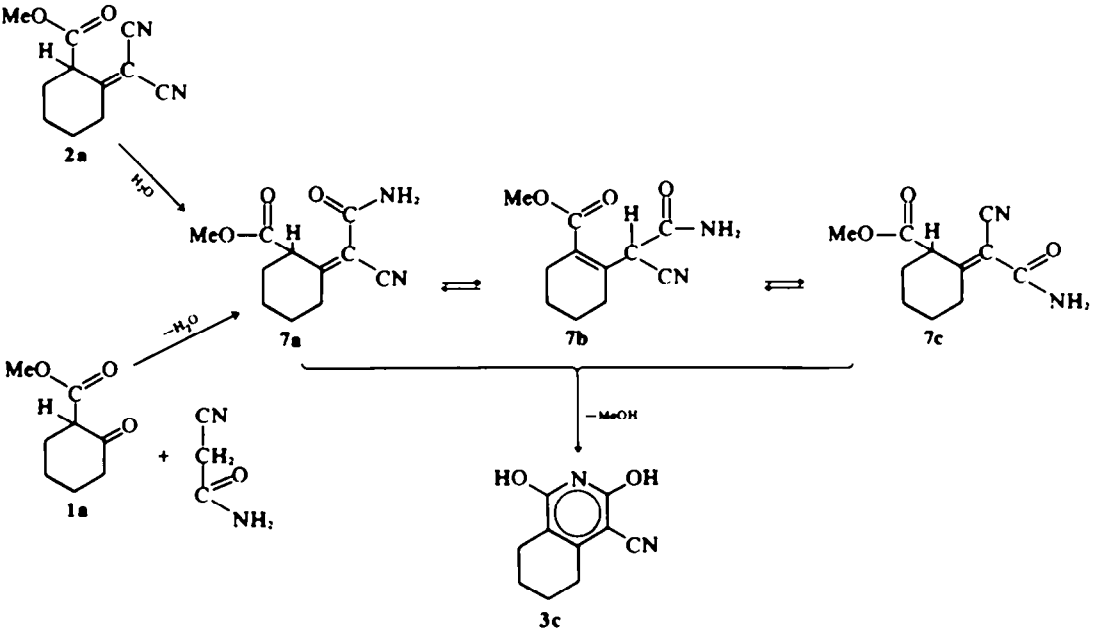
A most important and decisive piece of information regarding the structures of intermediates in the

*Addition of acetic acid in this experiment accelerated the reaction considerably.

†This conclusion is further supported by the observation that benzyl 2-dicyanomethylenecyclohexanecarboxlate yields **5** on careful catalytic hydrogenation, but not a trace of the obvious intermediate carboxylic acid nor of **6** could be detected.

cyclization reactions came from the observation, that boiling of **2a** in 98% ethanol induced the formation of small amounts of pyridinediol **3c**, presumably due to the presence of water. To enable the identification of the intermediates leading to this pyridinediol, **2a** was reacted with water in boiling dimethoxyethane (DME) and the reaction was monitored by UV spectroscopy and TLC. After 18 h the starting ester (λ_{max} 242 nm) had practically disappeared and had been converted to a compound with λ_{max} 232 nm and into pyridinediol **3c**. After 72 h **3c** was the only isolable reaction product.

The intermediate with λ_{max} 232 nm was isolated by means of TLC and identified (mainly on the basis of spectral data) as the amide **7**, i.e. a mixture of **7a**, presumably **7b**, and **7c** (Scheme 4).



SCHEME 4.

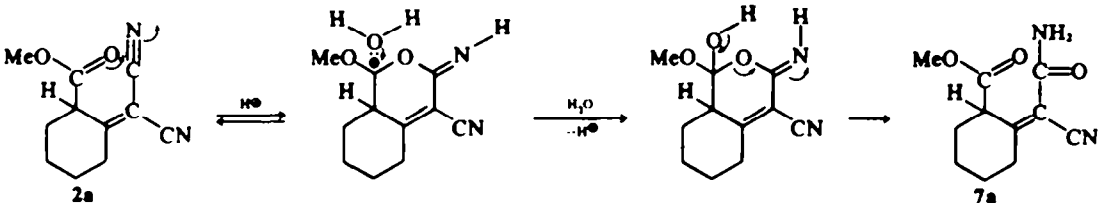
The same mixture of amides was also obtained in moderate yield by the Knoevenagel reaction of **1a** with cyanoacetamide in benzene. Heating the mixture, neat or in DME/H_2O solution, yielded **3c** in nearly quantitative yield.

Whereas the formation of pyridinediols from amides of type **7** is well documented,[4b,11,16] the hydrolysis of a nitrile to an amide under such mild conditions to our knowledge is without precedent.[12] Because the cyano groups of **5** are not hydrolyzed in boiling DME/H_2O, it is evident again that the ester group of **2a** plays an active part, this time in the formation of the amide group. **4a** shows no reaction under these conditions which is further proof of the activating influence of the second cyano group. Analogous to the conversion of **2c** to **6**, the interaction of the ester and dicyanomethylene group may be envisaged to consist of the formation of an oxygen bridge by nucleophilic attack of the carbonyl oxygen atom on one of the cyano groups (Scheme 5). Subsequent attack of water on the positive intermediate followed by ring opening to give amide **7a** would constitute a plausible mechanism for the facile hydrolysis of the cyano group.

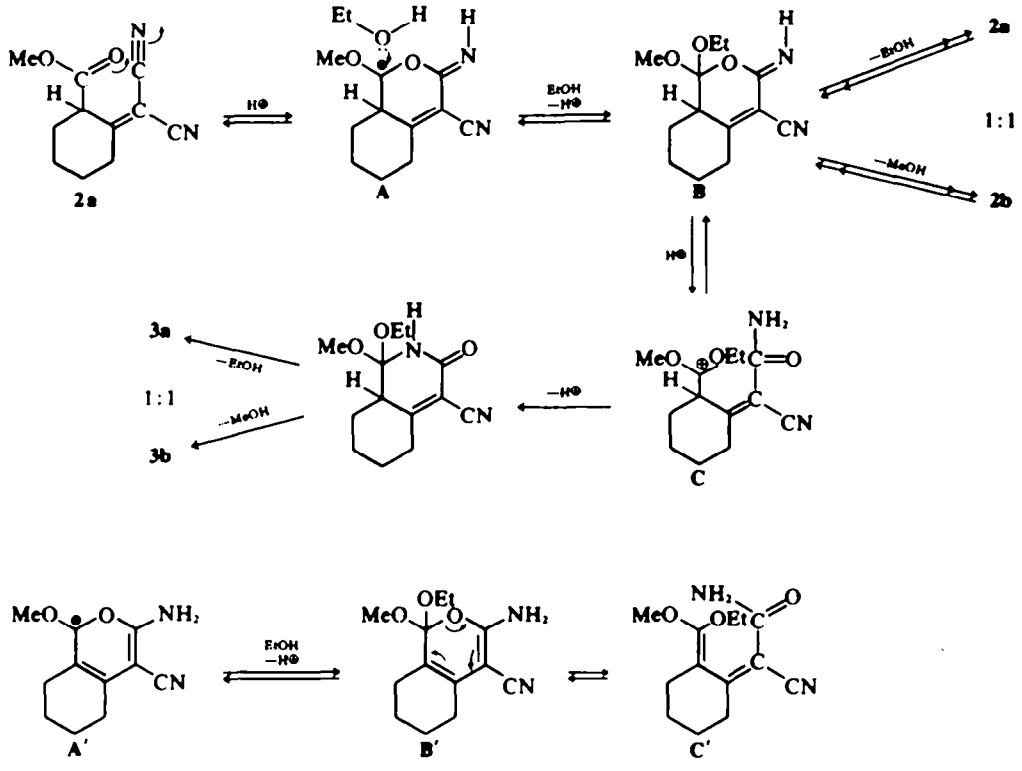
Mechanism of the formation of alkoxypyridinols

On the basis of the evidence for an electrophilic intermediate with oxygen bridge in the formation of **6** and **7**, the explanation of the transesterification and cyclization of **2a** in ethanol is straightforward (Scheme 6).

When ethanol takes over the role of water in Scheme 5, an intermediate **B** is formed which in a reverse reaction can either give back methyl ester **2a** or form ethyl ester **2b** in approximately equal amounts by extrusion of ethanol or methanol, respectively. Alternatively, the oxygen ring of the same intermediate **B** can be opened as postulated for the formation of **7** to give an intermediate **C** with an amide group, which can close to a nitrogen containing ring by intramolecular attack of the amido N atom on the positive C atom. Expulsion of either ethanol or methanol furnishes the alkoxypyridinols **3a** and **3b** in equal proportions as is found experimentally in the initial stages of the reaction.



SCHEME 5.



SCHEME 6.

If the proton on the cyclohexane ring adjacent to the ester group is removed in an early stage of the reaction sequence, the proposed mechanism is not changed essentially, because the new intermediates (e.g. A', B' and C' in Scheme 6) can be expected to react in an analogous fashion to provide **3a** and **3b**.

The function of the catalyst combination HOAc/NH_4OAc can now be accounted for. As indicated in Schemes 3, 5 and 6, acetic acid mainly catalyzes the formation of the intermediate **A** by further enhancement of the electrophilic character of the cyano group. The role of the basic component, presumably the acetate anion, can be interpreted as an attack on the intermediate **A** (as ethanol does in Scheme 6), thereby accelerating the conversion of **2a** to **3a** as a result of the better nucleophilic and leaving group properties of $AcO^{\ominus}$ as compared to EtOH and $EtO^{\ominus}$, respectively.[11] In accordance with this interpretation it was found, that the mixture of reaction products **3a** and **3b** obtained from **2a** in boiling ethanol *in the presence of ammonium acetate/acetic acid*, contained only 17% of ethoxypyridinol **3b** as compared to 89% in the "uncatalyzed" reaction (Table 1).

EXPERIMENTAL

All m.ps were determined on a Kofler hot stage apparatus under a Reichert microscope and are uncorrected. Unless otherwise stated, IR spectra were recorded in chloroform with a Perkin–Elmer 237 spectrophotometer, UV spectra in 96% EtOH with a Perkin–Elmer 137 spectrophotometer and NMR spectra in deuterated chloroform with a Varian A-60 spectrometer (chemical shifts relative to tetramethylsilane as an internal standard, $\delta = 0$ ppm). Mass spectral molecular weights were determined with a Varian Mat CH 5 spectrometer.

All reactions were performed with purified reagents in a nitrogen atmosphere.

Alkyl 2-oxocyclohexanecarboxylates **1a**, **1b**, **1c** were

prepared in 85% yield by Dieckmann cyclization of the corresponding dialkyl pimelates with NaH in dry benzene according to the method of Banerjee *et al.*[14]; 1c: b.p. 68–69°/1 mm; n_D^{21} 1·4711.

Alkyl 2-dicyanomethylenecyclohexanecarboxylates **2a, 2b, 2c.** A mixture of **1a, 1b** or **1c** (0·04 mole), malononitrile (0·044 mole), glacial AcOH (2·5 ml) and NH_4OAc (1·5 g) in benzene (40 ml) was stirred and heated to reflux with continuous removal of water (Wideqvist apparatus). After 3 h the light-brown soln was cooled and filtered, washed with water (3×) and dried over $MgSO_4$. Evaporation of the solvent yielded a yellow oil, which was purified by short-path distillation.

2a: yield 86%; b.p. 115–117°/0·5 mm; m.p. 56–57°; IR: 2235 (conj. CN, strong), 1740 (C=O), 1600 cm^{-1} (C=C, strong); UV: 242 nm (ε 13600); NMR: δ 1·2–3·3 (m, 8H, cyclohexane ring protons), 3·77 (s, 3H, CH_3O), 4·02 ppm (broad s, 1H, C=C–CH–COOR); mass spectrum: **2a**[+], Found 204·0886, Calc. for $C_{11}H_{12}N_2O_2$ 204·0899.

2b: yield 83%; b.p. 110–113°/0·05 mm; UV: 242 nm (ε 13400); NMR: δ 1·2–3·3 (m, 8H, cyclohexane ring protons), 1·28 (t, 3H, CH_3CH_2O), 4·00 (broad s, 1H, C=C–CH–COOR), 4·23 ppm (q, 2H, CH_3CH_2O); mass spectrum: **2b**[+], Found 218·1060, Calc. for $C_{12}H_{14}N_2O_2$ 218·1055.

2c: yield 59% (filtration of the crude reaction mixture yielded *ca* 30% of **6**); b.p. *ca* 140°/0·01 mm; IR: 2235 (conj. CN, strong), 1735 (C=O), 1600 cm^{-1} (C=C, strong); NMR: δ 1·47 (s, 9H, t-C_4H_9), 3·92 ppm (broad s, 1H, C=C–CH–COOR). (Found: C, 68·09; H, 7·47; N, 11·53. Calc. for $C_{14}H_{18}N_2O_2$: C, 68·27; H, 7·37; N, 11·38%).

1 - Alkoxy - 4 - cyano - 3 - hydroxy - 5,6,7,8 - tetrahydroisoquinoline **3a, 3b.** A magnetically stirred mixture of **1a** or **1b** (0·025 mole), malononitrile (0·027 mole), glacial AcOH (1·5 ml), NH_4OAC (300 mg) and benzene/(corresponding) alcohol 1:1 (35 ml) was heated to reflux for 36 h. Water was removed continuously by allowing the condensed vapours to flow back through 3 Å molecular sieves pellets into the reaction flask. At 4, 8, 18, and 24 h reaction time portions of each 100 mg of NH_4OAc were added.[15] Then the mixture was evaporated to dryness *in vacuo*, the residue taken up in boiling 1N NaOH (60 ml) and the resulting soln filtered rapidly. After cooling in ice the precipitated sodium salt of **3a** or **3b** was collected on a Buchner funnel, washed with a few ml of icecold 1N NaOH, suspended in water (75 ml) and acidified with conc HCl. The resulting ppt was cooled in ice, collected, washed with water, dried and recrystallized from benzene.

3a: yield 76%; m.p. 162–165° (dec); IR (Nujol): 3150 (OH, broad and strong), 2230 (conj. CN, very strong), 1605, 1580 (pyridine ring), no absorptions between 2230 and 1605 cm^{-1}; UV: 247 (ε 9900), 299 nm (ε 11700); NMR: δ 1·6–2·0 and 2·3–3·0 (2× m, 2×4H, cyclohexane ring protons), 4·02 (s, 3H, CH_3O), 9·0 ppm (broad s, 1H, OH). (Found: C, 64·76; H, 5·86; N, 13·75. Calc. for $C_{11}H_{12}N_2O_2$: C, 64·68; H, 5·92; N, 13·72%).

3b: yield 85%; m.p. 196–197° (dec); IR (Nujol): 3150 (OH, broad and strong), 2230 (CN, very strong), 1605, 1580 (pyridine ring), no absorptions between 2230 and 1605 cm^{-1}; UV: 247 (ε 10000), 299 nm (ε 12000); NMR: δ 1·6–2·0 and 2·3–3·0 (2× m, 2×4H, cyclohexane ring protons), 1·39 (t, 3H, CH_3CH_2O), 4·42 (q, 2H, CH_3CH_2O), 8·8 ppm (broad s, 1H, OH). (Found: C, 66·20; H, 6·50; N, 12·88. Calc. for $C_{12}H_{14}N_2O_2$: C, 66·03; H, 6·47; N, 12·84%).

4 - Cyano - 1,3 - dihydroxy - 5,6,7,8 - tetrahydroisoquinoline (**3c**) was synthesized as a reference substance from **1a** and cyanoacetamide according to the method of Wenkert *et al.*,[16] yield: 83%; m.p. 280–285° (dec) (lit.[16] m.p. 280–282°); IR (KBr): 3500–2200 (NH and OH, broad and strong), 2215 (CN, strong), 1660–1540 cm^{-1} (lactam); UV: 262 (ε 10000), 332 nm (ε 16500); NMR (D_6-DMSO): δ 9·77 ppm (broad s, 2H, NH and OH). (Found: C, 62·74; H, 5·39; N, 15·06. Calc. for $C_{10}H_{10}N_2O_2$: C, 63·14; H, 5·29; N, 14·73%). The same compound can be obtained in 75–80% yield from **3a** or **3b** by boiling for 18 h with a solution of KOH in ethylene glycol or by boiling with conc HCl.[2]

Ethyl 2-alkoxycarbonylcyclohexylidenecyanoacetates **4a, 4b** were prepared from **1a** or **1c** and ethyl cyanoacetate analogous to the procedure of Grewe *et al.*[4a]

4a: yield 72%; b.p. 111–112°/0·5 mm (lit.[4a] b.p. 150–157°/2 mm).

4b: yield 73%; b.p. 110–112°/0·1 mm.

Dicyanomethylenecyclohexane (**5**) was prepared from cyclohexanone and malononitrile according to the procedure of Prout,[17] yield: 97%; b.p. 144°/16 mm (lit.[17] b.p. 147–150°/15 mm); IR: 2235 (conj. CN, very strong), 1595 cm^{-1} (C=C, very strong); UV: 238 nm (ε 13700).

3 - Amino - 4 - cyano - 5,6,7,8 - tetrahydroisocoumarin (**6**). A soln of **2c** (492 mg, 2·0 mmole) and glacial AcOH (0·3 ml) in benzene/EtOH 1:1 (20 ml) was stirred and refluxed. After 20 h the mixture, containing a yellow ppt, was evaporated to dryness *in vacuo*. The resulting solid was stirred with $NaHCO_3$ aq, collected on a Buchner funnel, washed with water, dried *in vacuo* (giving 375 mg of yellow crystals) and recrystallized from EtOH, yielding 345 mg of **6**, yield: 91%; m.p. 204–205° (with rearrangement to **3c**); IR (KBr): 3310, 3155 (NH_2), 2210 (conj. CN, strong), 1710, 1650, 1610, 1555 cm^{-1}; UV: 267 (ε 14000), 337 nm (ε 12000); NMR (D_6-DMSO): δ 1·4–2·8 (m, 8H, cyclohexane ring protons), 8·3 ppm (broad s, 2H, NH_2). (Found: C, 63·33; H, 5·40; N, 14·85. Calc. for $C_{10}H_{10}N_2O_2$: C, 63·14; H, 5·29; N, 14·73%).

This compound was identical in all respects with the product obtained in 70% yield from the direct condensation of **1c** and malononitrile in benzene/EtOH, analogous to the synthesis of **3a** and **3b** (reaction time 20 h; work up procedure as described for the conversion **2c** → **6**).

2 - Methoxycarbonylcyclohexylidenecyanoacetamide (**7a, 7c**) *and 2 - methoxycarbonyl - 1 - cyclohexenylcyanoacetamide* (**7b**). A soln of **2a** (204 mg, 1 mmole) in DME (4 ml) and H_2O (1·5 ml) was boiled for 16 h. Then the mixture was evaporated *in vacuo* and partitioned between ether and sat $NaHCO_3$ aq [the aqueous layer, after acidifying with conc HCl, furnished 51 mg (27%) of **3c**]. The ether extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residual yellow oil (101 mg) (which according to TLC was already fairly pure) was purified by preparative TLC (SiO_2, $CHCl_3$/ether 3:2), yielding 44 mg of an oil (homogeneous in TLC with different eluents), whose IR and NMR spectra were almost identical with those of the crude product. On the basis of the following data, the oil was identified as a mixture of **7a, b, c**. IR: 3520, 3480, 3405, 3350, 3180 (NH_2), 2250 (unconj. CN, shoulder), 2220 (conj. CN, medium), 1730 (ester C=O), 1690, 1590 cm^{-1} (amide, very strong); UV: 232 nm (ε 10500); NMR: δ 1·2–3·25 (multiplets, almost identical with those of **2a** and **4a**, 8H, cyclohexane ring protons), 3·73, 3·77, and 3·82 (3× s, 3H, CH_3O), 3·95 and 5·18 (2× broad s, 1/4 H and 1/2 H, resp., C=C–CH–COOR of **7c** and **7a**, resp.), 5·65 (s, 1/4 H, CN–CH–$CONH_2$), 6·5 and 7·0 ppm (2× broad s, 3/4 H and 1/4 H, resp., NH_2 of **7a, c** and **7b**, resp.); molecular weight (determined with a Hewlett-Packard Vapor Pressure Os-

mometer 302 B): Found 226. Calc. for $C_{11}H_{14}N_2O_3$: 222.

Reaction of methyl 2-dicyanomethylenecyclohexanecarboxylate (**2a**) *in boiling ethanol.* Using the fact, that only **3a** and **3b** have absorption of 299 nm, the comparison of the ratio ($\epsilon_{\lambda_{max}}$ 240–250 nm/$\epsilon_{\lambda_{max}}$ 299 nm) of a sample of the reaction mixture with the same ratio of known mixtures of **2a** (**2b**) and **3a** (**3b**) proved to be a fairly accurate method for the determination of the degree of conversion of **2a** (**2b**) into **3a** + **3b**.

After the given time intervals (Table 1) the required amount of crude mixture were evaporated *in vacuo* and triturated with cold CCl_4. From the NMR spectra of the separated ppt and the CCl_4 filtrate, the composition of the mixture of pyridinols **3a** + **3b** and the extent of transesterification of **2a** to **2b**, respectively, could be determined. Alternatively, the samples obtained at 8, 14 and 20 h reaction time (Table 1), i.e. at low conversion to pyridinol, were evaporated to dryness *in vacuo*, taken up in ether and extracted with sufficient 0·1 N sodium sesquicarbonate solution (pH 10·1) to separate the relatively acidic pyridinols. By acidification of the aqueous layer with conc HCl and extraction with ether, the mixture of **3a** and **3b** was recovered and examined as above.

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