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KNOEVENAGEL CONDENSATION OF 2-CARBETHOXYCYCLOHEXANONE AND MALONONITRILE: SYNTHESIS OF 4-CYANO-3-ETHOXY-1-HYDROXY-5,6,7,8-TETRAHYDROISOQUINOLINE, AN ISOMER OF THE ABNORMAL PRODUCT

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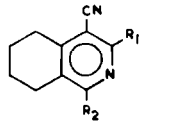
Abstract—The structure of the abnormal product **1a** formed in the Knoevenagel condensation of 2-carbethoxycyclohexanone and malononitrile has been further confirmed. Oxidation of the tetrahydroisoquinoline **3b** using Na_2Cr_2O–AcOH–H_2SO_4 gave the keto isoquinoline **3d** and the isoquinoline-1-carboxylic acid **5a**. The acid chloride of **5a** was condensed with diethyl ethoxymagnesiomalonate to afford after decarbethoxylation the methyl ketone **5d** which on Baeyer-Villiger oxidation gave a mixture of the acetate **1g** and the title compound **1b**. The unambiguous synthesis of **1b** confirms the structure assigned earlier to the title compound also formed during the partial hydrolysis of the diethoxy compound **1c**. Condensation of 2-acetylcyclohexane-1,3-dione with malononitrile gave the quinoline derivative **4c** which on ethylation yielded the ketoquinoline **4d**. The present studies have confirmed that the quinoline compound **4a** is also formed in the condensation of 2-acetylcyclohexanone and cyanoacetamide.

The tetrahydroisoquinoline structure **1a** has been assigned to the abnormal product obtained during the Knoevenagel condensation [NH_4OAc–AcOH, benzene–EtOH (1:1) or benzene as solvent] of 2-carbethoxycyclohexanone and malononitrile on the basis of spectral and degradation data.[1,2] The same product is also obtained by keeping 2-carbethoxycyclohexylidenemalononitrile **2** at room temperature for several days.[2] A novel mechanistic feature of this reaction is the retention of the OEt of the ester group during cyclization of the intermediate **2**. Ethylation of **1a** gives the diethoxy compound **1c**, which on partial hydrolysis using KOH in ethylene glycol gives again **1a** and another compound which must have the isomeric structure†, *viz*, 4-cyano-3-ethoxy-1-hydroxy-5,6,7,8-tetrahydroisoquinoline **1b**. We now present confirmatory evidence in favour of the structures **1a** and **1b**.

The OH group of the abnormal product **1a** was removed to give a compound to which the structure **1d** has been assigned earlier.[1b] A compound having the structure **1f** should have resulted from the degradation experiment if the abnormal product had the isomeric structure **1b**. An authentic sample of **1f** was prepared by ethylation of the known compound **1e**[3] using the Ag-salt method[4] and was found to be different from the degradation product‡ **1d** as evident by a comparison of the spectral data and mixed m.p. determination. It is significant that the NMR spectrum of **1f** shows a one proton singlet at 7·91δ whereas the proton singlet due to the aromatic hydrogen of **1d** is reported† to appear at 8·23δ. The comparative downfield shift of the C-3 proton in the structure **1d** is evidently due to the electron-withdrawing cyano group at C-4 and lends further support to the assigned structure **1d**. The structure of the abnormal product of Knoevenagel condensation must, therefore, be 4 - cyano - 1 - ethoxy -



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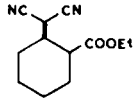
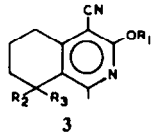


2

a: R_1 = OH; R_2 = OEt
b: R_1 = OEt; R_2 = OH
c: $R_1 = R_2$ = OEt
d: R_1 = H; R_2 = OEt
e: R_1 = OH; R_2 = H
f: R_1 = OEt; R_2 = H
g: R_1 = OEt; R_2 = OAc
h: R_1 = OAc; R_2 = OEt



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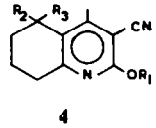


4

a: $R_1 = R_2 = R_3$ = H
b: R_1 = Et; $R_2 = R_3$ = H
c: R_1 = H; $R_2 = R_3$ = O
d: R_1 = Et; $R_2 = R_3$ = O

†Consequent upon the revision of the structure of the abnormal condensation product to **1a** by Bickelhaupt and Van der Baan,[1b] the initially proposed structure[1a] for this isomeric compound stands revised to **1b**.

‡We thank Prof. Bickelhaupt and Dr. Van der Baan for providing us with the details of the degradation experiment and the NMR data for **1d**, prior to publication.

3 - hydroxy - 5,6,7,8 - tetrahydroisoquinoline **1a** as suggested earlier. This has been further confirmed by an alternate synthesis (*vide infra*).

A confirmation of the structure of **1b** has been obtained by an unambiguous synthesis. The sequence of reactions used for the synthesis are shown in Scheme 1.

Sen *et al.*[5] have reported that condensation of 2-acetylcyclohexanone and cyanoacetamide in the presence of diethylamine results in a mixture of the isoquinoline compound **3a** and the quinoline compound **4a**. However, Freeman *et al.*[6] have recently concluded on the basis of spectral data and degradation studies that the above condensation results in the exclusive formation of **3a**. Whereas Sen *et al.*[5] used equimolar quantities of 2-acetylcyclohexanone and cyanoacetamide (conditions A), Freeman *et al.*[6] have used only one-half mole of cyanoacetamide for one mole of 2-acetylcyclohexanone (conditions B). We have been able to show conclusively (*vide infra*) that under both the conditions, a mixture of the isoquinoline compound **3a** and the quinoline compound **4a** (minor product) is indeed formed, but to different extent.

The crude condensation product prepared under conditions A was ethylated using the Ag-salt method[4] to give the crude material* melting over a wide range (87–108°). Crystallization, however, afforded a sharp melting compound (114–5°). Similar ethylation of the crude condensation product prepared under conditions B gave the isoquinoline compound **3b** (m.p. 114–5°) after crystallization (m.p. of the crude product* 109–13°) which was identical with the compound mentioned above.

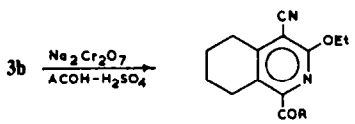
Oxidation[7] of methyl pyridines to the corresponding aldehydes or acids is well-known. However, oxidation of the compound **3b** by the reported methods using SeO_2, $KMnO_4$ (neutral) or ceric ammonium nitrate failed to give any appreciable amount of keto compounds. Oxidation was finally accomplished using a mixture of $Na_2Cr_2O_7$–AcOH–H_2SO_4. The acidic portion of the oxidation product gave, after purification, the required acid **5a** in about 3% yield. The structure of the acid was confirmed by its spectral data and by chemical transformations. In the IR spectrum (nujol), the bands at 3650–3200 (b), 2800–2500 (b) (intermolecularly bonded OH), 3340 (free OH) and 1745 cm^{-1} (C=O) indicated the presence of a carboxylic group. The presence of the nitrile was confirmed by a band at 2240 cm^{-1}. The NMR spectrum ($CDCl_3$) showed signals at 1·50 (*t*, J = 7 Hz, 3H, $-CH_2-CH_3$), 1·70–2·03 (*m*, 4H, $-CH_2-CH_2-$), 2·90–3·40 (*m*, 4H, benzylic), 4·53 (*q*, J = 7 Hz, 2H, $-OCH_2-CH_3$) and 10·23δ (*bs*, 1H, exchangeable with D_2O, –COOH). Esterification of the acid with diazomethane gave the corresponding Me ester **5b** which showed carbonyl absorption at 1752 cm^{-1} in its IR spectrum (nujol) and the carbomethoxy signal at 3·90 δ in the NMR spectrum. The structure of the acid was further confirmed by its decarboxylation using Cu-quinoline to the isoquinoline compound **1f** mentioned earlier. This further supports the isoquinoline structure assigned to **3a** earlier.

The neutral portion of the above oxidation product consisted of a mixture of a ketone and the starting material **3b** which could be separated by chromatography over neutral alumina. The IR spectrum of the ketone showed a peak at 1680 cm^{-1} characteristic of a conjugated CO group. Its NMR spectrum (CCl_4) showed signals at 1·47 (*t*, J = 7 Hz, 3H, $-CH_2-CH_3$), 2·00–2·40 (*m*, 2H, $-CH_2-CH_2-CH_2-$), 2·63 (*t*, J = 6 Hz, 2H, benzylic), 2·77 (*s*, 3H, CH_3), 3·10 (*t*, J = 6 Hz, 2H, $-COCH_2-CH_2-$) and 4·55δ (*q*, J = 7 Hz, 2H, $-OCH_2-CH_3$). The downfield shift of the Me signal (2·77δ) compared to that in the starting material (2·36δ) clearly indicated that the oxidation had occurred at 8-position. On the basis of these spectral data, the ketone has been assigned the structure, 4 - cyano - 3 - ethoxy - 1 - methyl - 8 - oxo - 5,6,7,8 - tetrahydroisoquinoline **3d**.

Initially, very pure ethoxypyridine **3b**, m.p. 114–5°, was employed in the oxidation experiment. Later, when the oxidation was carried out using crude ethoxypyridine (m.p. 87–108°) prepared as mentioned before, in addition to the acid **5a**, two compounds with very close R_f† values in TLC were obtained in the neutral fraction. These were separated by column chromatography followed by preparative TLC and crystallization.

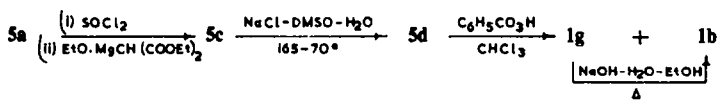
*The amount of N-ethylated compound was extremely small as indicated by a very weak absorption at 1650 cm^{-1} in the IR spectrum.

†R_f values 0·73 and 0·67 in solvent system light petroleum-ethyl acetate (4:1).



5

a: R = OH; **c**: R = $CH(COOEt)_2$
b: R = OMe; **d**: $R = CH_3$

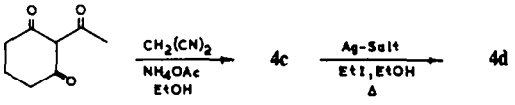


SCHEME 1

The compound with higher R_f value (0·73 was shown to be identical with the ketone **3d** (IR, mixed m.p.). The lower R_f value (0·67) compound, m.p. 92–3°, also showed the presence of a conjugated carbonyl (1690 cm^{-1}) in the IR spectrum. The NMR spectrum of this ketone was very similar to that of the ketone **3d**. These spectral properties could be explained only in terms of the isomeric keto quinoline structure **4d**.

The structure of this ketone was further confirmed by an alternate synthesis as shown in Scheme 2.

Condensation of substituted 2 - acetylcyclohexane - 1,3-diones with malononitrile has been studied[8] earlier and is reported to give quinoline derivatives. In the present case, the condensation of 2-acetylcyclohexane-1,3-dione with malononitrile was carried out in the presence of NH_4OAc and EtOH to give the hydroxy ketone **4c** which showed peaks at 3300–2300 (*b*, OH), 2235 (C≡N), 1680 (C=O), 1650 (CONH) and 1585 (C=C) cm^{-1} in the IR spectrum (nujol). It was ethylated using the Ag-salt method[4] to give the compound **4d** identical (IR, mixed m.p.) with the ketone obtained in the above oxidation.



SCHEME 2

As mentioned earlier, the ketone **4d** was formed only when the crude ethoxy compound (m.p. 87–108°) was employed for oxidation. This clearly indicates that it results from the quinoline compound **4b** present in the crude ethylation product. The quinoline derivative **4b**, in turn, is formed from the corresponding hydroxy compound **4a** which is one of the products formed under conditions A. To estimate* roughly the amount of the quinoline compound **4a** formed in the above condensation under conditions A, in one of the experiments, the crude ethylation product (m.p. 87–108°) was crystallized and the crystallized sample as well as the residue obtained from the mother liquor were separately oxidized. The latter gave rise to a mixture of ketones which were separated as mentioned before. The quinoline ketone **4d** was, thus, obtained in an overall yield of 7%, thereby indicating that during the condensation of equimolar quantities of 2-acetylcyclohexanone and cyanoacetamide (conditions A), the quinoline compound **4a** is formed in at least 7% yield. This confirms the earlier findings of Sen *et al.*[5] However, the crude ethoxy compound (m.p. 109–13°) referred to earlier, gave very minute amount of the quinoline ketone **4d**, thus indicating that under conditions B, the quinoline compound **4a** is formed in extremely small quantities.

The acid **5a** was converted into its acid chloride. The crude acid chloride was condensed with diethyl ethoxymagnesiomalonic ester to furnish the crude β-keto ester **5c** which on decarbethoxylation[9] gave the methyl ketone **5d** in about 50% yield. The spectral properties [IR: 1698 cm^{-1} (C=O) and NMR: 2·65δ (*s*, 3H, $COCH_3$)] of this compound confirmed its structure. Baeyer-Villiger oxidation of this ketone gave a mixture of the acetate **1g** and a hydroxy compound which were separated by chromatography. The structure of the acetate was evident from its IR ($OCOCH_3$, 1785 cm^{-1}) and NMR ($OCOC\underline{H}_3$, 2·33δ) spectra. It was identical (IR, mixed m.p.) with the acetate prepared from the hydroxy compound **1b**. The isomeric acetate **1h** differed significantly (TLC, IR and m.p.) from **1g**.

Hydrolysis of the acetate **1g** using aqueous ethanolic sodium hydroxide gave the corresponding OH compound identical (IR, mixed m.p.) with the hydroxy compound obtained in the Baeyer-Villiger oxidation of **5d**. Further, it was identical with the hydroxy compound **1b** mentioned earlier. The synthesis of **1b**, thus, confirms the structure of one of the hydrolysis products (**1b**) of the diethoxy compound **1c** and also of the abnormal condensation product **1a** referred to earlier.

*Due to lack of facilities, a quantitative estimation using GLC could not be carried out.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. UV spectra were recorded in 95% EtOH on a Beckmann Unicam SP700A spectrophotometer and IR spectra on a Perkin-Elmer Model 700 or Carl-Zeiss UR10 spectrophotometers. NMR spectra were taken on a Varian HA100D or T-60 spectrometers using TMS as internal standard. Mass spectrum was recorded on an Atlas CH-4 spectrometer equipped with a direct inlet system. All chemical shifts are reported in δ values. Light petroleum refers to fraction b.p. 40–60°. All solvent extracts were dried over Na_2SO_4.

4-Cyano-3-ethoxy-5,6,7,8-tetrahydroisoquinoline **1f**

To a soln of **1e** (0·58 g, 0·033 mole) prepared according to the lit method[3] in KOHaq (0·19 g in 10 ml water), a soln of $AgNO_3$ (0·6 g, 0·035 mole) was added with stirring. The Ag-salt, thus obtained, was filtered, washed well with water, EtOH and dried. The suspension of the dry Ag-salt in absol. EtOH (20 ml) containing EtI (0·62 g, 0·040 mole) was refluxed for 6 hr with stirring, filtered while hot, and the residue was washed well with hot EtOH. The solvent was removed from the filtrate to afford a residue which was taken up in ether-benzene mixture and washed with 5% ice-cold NaOH (4 × 15 ml), water (4 × 15 ml) and dried. The residue (350 mg) obtained after removal of the solvent was crystallized from hexane to furnish **1f**, m.p. 82–3° IR (nujol): ν_{max} 2230 cm^{-1} (C≡N); UV: λ_{max} 233 (ϵ 6240) and 307 nm (5140); NMR (CCl_4): 1·44 (*t*, J = 7 Hz, 3H, $-OCH_2\underline{CH}_3$), 1·68–2·04 (*m*, 4H), 2·60–2·80 (*m*, 2H), 2·80–3·04 (*m*, 2H), 4·42 (*q*, J = 7 Hz, 2H, $-OCH_2CH_3$) and 7·91 (*s*, 1H, ar H). (Found: C, 71·34; H, 6·96; N, 14·20. $C_{12}H_{14}N_2O$ requires: C, 71·26; H, 6·98; N, 13·85%).

Condensation of 2-acetylcyclohexanone and cyanoacetamide

(a) Condensation was carried out as reported by Sen *et al.*[5] Thus, 2-acetylcyclohexanone[10] (28 g, 0·20 mole), cyanoacetamide (16·8 g, 0·20 mole) and diethylamine (3·5 ml) gave the crude condensation product (33 g). (b) Condensation of 2-acetylcyclohexanone (4·6 g, 0·037 mole) and cyanoacetamide (1·5 g, 0·0175 mole) using diethylamine (0·5 ml) according to Freeman *et al.*[6] gave the crude condensation product (2·8 g).

4-Cyano-3-ethoxy-1-methyl-5,6,7,8-tetrahydroisoquinoline **3b**

The crude condensation product (37·6 g) prepared under (a) was ethylated following the method described above for the prepara-

tion of **1f**, using NaOH (8·2 g), $AgNO_3$ (36 g), EtI (36 g) and absol. EtOH (350 ml). The crude ethylated product (33 g, m.p. 87–108°) was crystallized from EtOH to get pure **3b** (24 g), m.p. 114–5°. IR (nujol): ν_{max} 2230 cm^{-1} (C≡N); UV: λ_{max} 238 (ϵ 7080) and 308 nm (7160); NMR (CCl_4): 1·43 (*t*, J = 7 Hz, 3H, $-OCH_2-\underline{CH_3}$), 1·67–2·00 (*m*, 4H, $-\underline{CH_2}-CH_2-$), 2·36 (*s*, 3H, Me), 2·43–2·70 (*m*, 2H, benzylic), 2·72–3·00 (*m*, 2H, benzylic) and 4·44 (*q*, J = 7 Hz, 2H, $-O\underline{CH_2}-CH_3$) (Found: C, 72·20; H, 7·53, N, 13·22. $C_{13}H_{16}N_2O$ requires: C, 72·22, H, 7·40, N, 12·96%).

The solvent was removed from the mother liquor and the residue thus obtained (9 g) was used for oxidation (*vide infra*).

The starting material (1·2 g) was recovered after acidification of the alkali washings.

Similarly, ethylation of the crude condensation product (1·8 g) obtained under (b) gave the crude ethylated product (1·65 g) m.p. 109–13°. Crystallization from EtOH gave pure **3b**, m.p. 114–5°. The starting material (0·2 g) was recovered.

4 - Cyano - 3 - ethoxy - 5,6,7,8 - tetrahydroisoquinoline - 1 - carboxylic acid **5a** *and 4 - cyano - 3 - ethoxy - 1 - methyl - 8 - oxo - 5,6,7,8 - tetrahydroisoquinoline* **3d**

To a stirred soln of **3b** (24 g, 0·11 mole) in a mixture of gl AcOH (245 ml) and conc H_2SO_4 (18 ml), $Na_2Cr_2O_7 \cdot 2H_2O$ (50 g, 0·165 mole) was added, in small portions over a period of about 2 hr so that the temp did not rise above 60°. Stirring was continued for another 10 hr at room temp. Water (~1·5 l) was added and the mixture was extracted with benzene-ether (1 : 1) (4 × 250 ml). The combined organic extract was successively washed with water (6 × 100 ml), 10% Na_2CO_3aq (8 × 60 ml), water (4 × 100 ml) and dried. Removal of the solvent gave a dark-brown residue (18·2 g) which was chromatographed over neutral alumina (500 g). Elution with light petroleum gave the unreacted **3b** (4·5 g) followed by a mixture of **3b** and the ketone **3d** (0·4 g). Further elution with benzene gave ketone **3d** (11·0 g) which was crystallized from hexane, m.p. 91–2°. IR (nujol): ν_{max} 1680 (C=O) and 2230 (C≡N) cm^{-1}. UV: λ_{max} 228 (ϵ 8700), 269 (3750), 288 (2550) and 296 nm (2100). (Found: C, 67·81; H, 6·03; N, 12·40. $C_{13}H_{14}N_2O_2$ requires: C, 67·81; H, 6·13; N, 12·17%).

Acidification of the Na_2CO_3 washings with dil HCl gave a crude acid (700 mg) as light brown solid. It was purified by chromatography over Si-gel (20 g). Elution with benzene gave a colourless solid which on crystallization from EtOH–H_2O furnished **5b** as colorless needles (450 mg) m.p. 139–40°. UV: λ_{max} 222 (6850), 242 (2090) and 316 nm (2540). (Found: C, 63·71; H, 5·35; N, 11·34. $C_{13}H_{14}N_2O_3$ requires: C, 63·40; H, 5·73; N, 11·38%).

Esterification of **5a** (200 mg) using an ethereal soln of diazomethane gave **5b** (200 mg) which was crystallized from hexane, m.p. 90–91°. IR (nujol): ν_{max} 2225 (C≡N), and 1752 (COOMe) cm^{-1}; UV: λ_{max} 218 (ϵ 6590), 238 (1650) and 312 nm (1900); NMR (CCl_4): 1·47 (*t*, J = 7 Hz, 3H, $-OCH_2\underline{CH_3}$), 1·67–2·00 (*m*, 4H, $-\underline{CH_2}-CH_2-$), 2·66–3·13 (*m*, 4H, benzylic), 3·90 (*s*, 3H, COOMe) and 4·50 (*q*, J = 7 Hz, 2H, $-O\underline{CH_2}-CH_3$). (Found: C, 64·68; H, 6·20, N, 10·67. $C_{14}H_{16}N_2O_3$ requires: C, 64·60; H, 6·20; N, 10·76%).

Decarboxylation of **5a**. A mixture of **5a** (100 mg), Cu-powder (20 mg) and quinoline (1·5 ml) was heated at 230–50° for 4 hr, cooled, acidified with 10% HCl and extracted with ether (3 × 10 ml), washed with water (3 × 5 ml) and dried. Solvent removal followed by preparative TLC of the residue gave a solid (12 mg) identical (IR, m.p.) with an authentic sample of **1f**.

3 - Cyano - 2 - hydroxy - 4 - methyl - 5 - oxo - 5,6,7,8 - tetrahydroquinoline **4c**

A mixture of 2-acetylcyclohexane-1,3-dione[8] (462 mg, 3 mmoles), malononitrile (198 mg, 3·1 mmole), NH_4OAc (300 mg) and absol. EtOH (10 ml) was refluxed for 12 hr, EtOH was removed under suction and water was added to the residue. The yellow solid obtained was filtered, washed well with water and dried (170 mg). Crystallization from MeOH gave **4c**, m.p. 292–3° *d* as small yellow needles. UV: λ_{max} 220 (8970), 226 sh (8610), 284 (7450) and 328 nm (5920). (Found: C, 65·39; H, 4·78; N, 14·11. $C_{11}H_{10}N_2O_2$ requires: C, 65·34; H, 4·98; N, 13·85%).

3 - Cyano - 2 - ethoxy - 4 - methyl - 5 - oxo - 5,6,7,8 - tetrahydroquinoline **4d**

(a) The solid residue (9·0 g) obtained from the mother liquor during preparation of **3b** (*vide supra*) was oxidized using $Na_2Cr_2O_7 \cdot 2H_2O$ (19·1 g), AcOH (95 ml) and conc H_2SO_4 (6·8 ml). Column chromatography of the crude product mixture gave the starting material (2·10 g), a mixture of the ketones **3d** and **4d** (3·10 g) and the ketone **4d** (0·51 g). **4d** was crystallized from hexane, m.p. 92–3°. Preparative TLC of a portion (200 mg) of the above ketone mixture gave **3d** (80 mg) and **4d** (85 mg), thus amounting to about 7% yield of **4d** on the basis of the crude ethylated product (conditions (a)). IR (nujol): ν_{max} 2230 (C≡N), 1690 (C=O) and 1565 cm^{-1}; UV: λ_{max} 228 (ϵ 6000), 268 (2810), 294 (1690) and 305 nm (1790). (Found: C, 68·08; H, 6·13; N, 11·68. $C_{13}H_{14}N_2O_2$ requires: C, 67·81; H, 6·13; N, 12·17%).

(b) *By ethylation of* **4c**. Ethylation of **4c** (142 mg) using the Ag-salt method described earlier gave the crude product (65 mg) which on preparative TLC (45 mg) followed by crystallization from hexane gave **4d**, m.p. 92–3°, identical (IR, mixed m.p.) with the above compound.

1-Acetyl-4-cyano-3-ethoxy-5,6,7,8-tetrahydroisoquinoline **5d**

(i) *Acid chloride of* **5a**. A mixture of **5a** (615 mg) and $SOCl_2$ (2·5 ml) was refluxed for 2 hr. Excess of $SOCl_2$ was removed under suction. Benzene was added to the residue and the solvent was removed again. The crude residue (IR: no OH, COCl 1765 cm^{-1}) was used in the next step.

(ii) *Condensation with diethyl ethoxymagnesiomalonate*. The crude acid chloride was condensed with diethyl ethoxymagnesiomalonate following a general procedure[11] using diethyl malonate (430 mg) and Mg-turnings (65 mg) to give, after work-up, a yellow viscous residue (**5c**, 1·01 g) which was used for the next step without further purification.

(iii) *Decarbethoxylation of* **5c**. A mixture of crude **5c** (1·01 g), NaCl (310 mg), water (0·3 ml) and DMSO (5 ml) was stirred and heated at 165–70° for 4 hr by which time there was no more CO_2 evolution. It was cooled, water (100 ml) was added and the mixture was extracted with ether-benzene (1 : 1)(4 × 50 ml), washed with water (2 × 20 ml) and dried. Solvent removal gave a dark brown residue (660 mg) which was chromatographed over neutral alumina (15 g). Elution with light petroleum-benzene (2 : 1) gave the crude ketone (445 mg) which was purified by preparative TLC to afford **5d** (400 mg) as an oil, IR (neat): ν_{max} 2235 (C≡N) and 1698 (C=O) cm^{-1}; UV: λ_{max} 246 (ϵ 2980), 324 (3780); NMR ($CDCl_3$): 1·47 (*t*, J = 7 Hz, 3H, $-OCH_2\underline{CH_3}$), 1·66–2·00 (*m*, 4H, $-\underline{CH_2}-CH_2-$), 2·65 (*s*, 3H, $COCH_3$), 2·80–3·17 (*m*, 4H, benzylic) and 4·53 (*q*, J = 7 Hz, 2H, $-O\underline{CH_2}-CH_3$). (Found: N, 11·32. $C_{14}H_{16}N_2O_2$ requires: N, 11·47%).

Baeyer-Villiger oxidation of **5d**

Preparation of 4 - cyano - 3 - ethoxy - 5,6,7,8 - tetrahydroisoquinoline - 1 - acetate **1g** *and 4 - cyano - 3 - ethoxy - 1 - hydroxy - 5,6,7,8 - tetrahydroisoquinoline* **1b**. A soln of **5d** (265 mg) in a freshly prepared soln of perbenzoic acid[12] in $CHCl_3$ (6 ml) was allowed to stand at room temp for 120 hr with occasional swirling. $CHCl_3$ (15 ml) was then added and the soln was washed with $NaHCO_3$aq (1M, 4 × 5 ml), water (4 × 10 ml) and dried. Removal of $CHCl_3$ under vacuum gave a residue (350 mg) which was chromatographed over neutral alumina (10 g). Elution with benzene gave a mixture (105 mg) consisting mainly of the starting material and an acetate which were separated by preparative TLC

using the solvent system, light petroleum-ethyl acetate (11:1) to afford unreacted **5d** (49 mg) and the acetate **1g** (20 mg). The acetate was crystallized from absol. EtOH, m.p. 101–2°. IR: ν_{max} 1775 ($OCOCH_3$) and 2245 (C≡N) cm^{-1}; UV: λ_{max} 238 (2080) and 300 nm (2600); NMR ($CDCl_3$): 1·40 (*t*, J = 7 Hz, 3H, $-CH_2-\underline{CH_3}$), 1·72–1·98 (*m*, 4H, $-CH_2-CH_2-$), 2·33 (*s*, 3H, $-OCOCH_3$), 2·40–2·60 (*m*, 2H, benzylic), 2·80–3·00 (*m*, 2H, benzylic) and 4·43 (*q*, J = 7 Hz, 2H, $-O\underline{CH_2}-CH_3$). (Found: C, 64·91; H, 6·46; N, 10·98. $C_{14}H_{16}N_2O_3$ requires: C, 64·60; H, 6·20; N, 10·76%). $CHCl_3$ elution gave a mixture (25 mg) consisting mainly of the acetate **1g** and the compound **1b**. Further elution with EtOH gave pure **1b** (90 mg) which was crystallized from benzene as colorless needles, m.p. 179–80° (Reported[1a] 176–77°). IR: ν_{max} 2380–3500 (br, OH), 2225 (C≡N) and 1600 cm^{-1}. UV: λ_{max} 248 (8640) and 302 nm (11,570); NMR ($CDCl_3$): 1·43 (*t*, J = 7 Hz, 3H, $-CH_2-\underline{CH_3}$), 1·63–2·03 (*m*, 4H), 2·27–2·67 (*m*, 2H), 2·67–3·00 (*m*, 2H) and 4·48 (*q*, J = 7 Hz, 2H, $-O-\underline{CH_2}-CH_3$). Mass spectral fragments: *m/e* 218 (M^+), 203 ($M-CH_3$), 190 (M, $-C_2H_4$ or CO, *m** 165·8, 189 ($M-C_2H_5$), 175 (190–CH_3), *m** 161), 162 (190–CO or C_2H_4, *m** 138·2) and 134 (162–CO or C_2H_4, *m** 111)(Found: N, 13·20; $C_{12}H_{14}N_2O_2$ requires: N, 12·84%).

Hydrolysis of the acetate **1g**. A soln of **1g** (25 mg) in ethanolic (1:1) NaOH aq (20 mg, 2 ml) was heated on a water-bath for 15 min, cooled and acidified with dil HCl. The fluffy solid obtained was filtered, washed with water and dried to give **1b** (13 mg) identical (IR, mixed m.p.) with the hydroxy compound obtained in the Baeyer-Villiger oxidation.

Preparation of **1g** *from* **1b**. A mixture of **1a** (95 mg) and Ac_2O (1·5 ml) was refluxed for 2 hr and Ac_2O was removed under suction. Absol. EtOH (2 ml) was then added to the residue and the solvent was removed again under suction. The residue (100 mg) was crystallized from absol. EtOH to get **1g**, m.p. 101–2°, identical (IR, mixed m.p.) with a synthetic sample of the acetate.

4 - *Cyano* - 1 - *ethoxy* - 5,6,7,8 - *tetrahydroisoquinoline* - 3 - *acetate* **1h**

Acetylation of **1a** (430 mg) was carried out as before using Ac_2O (3 ml). The crude acetate was crystallized from absol. EtOH to get pure **1h**, m.p. 92–3°. IR (nujol): ν_{max} 1790 ($OCOCH_3$) and 2235 cm^{-1} (C≡N); UV: λ_{max} 249 (ε 6990), 280 (4430) and 324* (970) nm; NMR (CCl_4): 1·37 (*t*, J = 7 Hz, 3H, $-CH_2-\underline{CH_3}$), 1·71–1·94 (*m*, 4H, $-CH_2-CH_2-$), 2·33 (*s*, 3H, $OCOCH_3$), 2·45–2·64 (*m*, 2H, benzylic), 2·75–2·93 (*m*, 2H, benzylic) and 4·36 (*q*, J = 7 Hz, 2H, $-O\underline{CH_2}-CH_3$). (Found: C, 64·57; H, 6·15; N, 10·78. $C_{14}H_{16}N_2O_3$ requires: C, 64·60; H, 6·20; N, 10·76%).

*This band probably arises from small amounts of **1a** formed by hydrolysis of **1h** in 95% EtOH.

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