PHOTOLYSIS OF 2,6-DIMETHYL-3,5-DICARBOETHOXY-1,4-DIHYDROPYRIDINE-4-CARBOXYLIC ACID

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Abstract—The photolysis of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine-4-carboxylic acid **1** gives with a pyrex filter pyridine **2** and glycol **3**. At low concentration, aldehyde **4** accumulates. The photochemical dimerization of this aldehyde gives glycol **3** in methanol or ethanol. The aldehydic hydrogen in aldehyde **4** is replaced by deuterium on performing the photolysis of acid **1** in MeOD as is the case for the photolysis of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine. A concerted mechanism for the decarboxylation of acid **1** to aldehyde **4** is possible. When the photolysis of **1** is performed in quartz, another reaction occurs leading to 1,2-dihydropyridine **8**.

THE PHOTOLYSIS of 1,4-dihydropyridines with electron attracting groups (—COMe —NO$_2$, —CO$_2$R for example) in position(s) C-3 or C-3 and C-5 is a subject of study in several laboratories. The observed photochemical reactions are of two principal types:

(i) dimerization[1] involving the 2,3 and 5,6 double bonds, or migration of the double bonds to form isomeric dihydropyridines:[1, 2]

(ii) oxidation of the dihydropyridine system to a pyridine, with or without simultaneous reduction of an adjacent group (—NO$_2$[3], —COMe[1]).

In addition, a recent study has been carried out on the related pyridine-3,5-diesters.[4] The authors isolated mainly the corresponding dihydropyridines which result either from the addition of solvent (MeOH or EtOH) or from a photoreduction (1,4-dihydropyridines).

The large diversity of thermal reactions[5] for the 2,6-dimethyl-1,4-dihydropyridine-4-carboxylic acids substituted at positions C-3 and C-5 by —CO$_2$Et, —CN, —COCH$_3$ etc. led us to investigate their photolysis.

We present here the results of photolysis of 2,6-dimethyl 3,5-dicarboethoxy 1,4-dihydropyridine 4-carboxylic acid **1**, the structure proofs of the products and a discussion of the probable mechanisms involved.
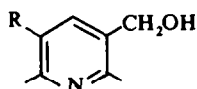
Products of the photolysis of **1**

Photolysis of **1** in various solvents (MeOH, EtOH, t-BuOH, dioxane) either in pyrex or in quartz, gave, as major products **2** to **8** and, in trace amounts **9** and **10**,
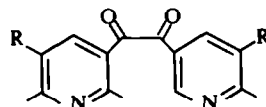

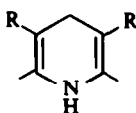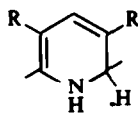|		
1	**2**	**3**
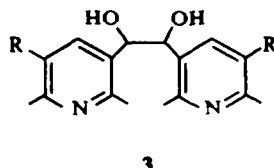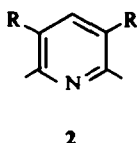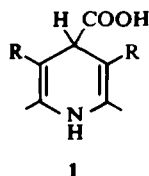
* Laboratoire Associé au C.N.R.S.
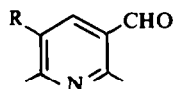
R = COOEt **7**

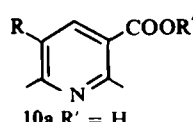**10a** R' = H
b R' = Me

The following table brings together results obtained under the various conditions:

Solvent	Filter	Time of irradiation (hours)	Concentration M/l	Product Yields								
				2	3	4	5	6	7	8	9	10a[a]
	pyrex	96	—	77								[b]
McOH	pyrex	64	0·66	41	55	0·2	0·6				1·5	0·2 [c]
EtOH	pyrex	24	0·05	18	36							[d]
t-BuOH	pyrex	24	0·03	28	10			18				
dioxane[e]	pyrex	24	0·085	26	6	trace		17				
dioxane[f]	pyrex	64	0·056	34	5	6	3	8			2	[g]
MeOH	quartz	10	0·034	16	13		7·5		3	4*		
EtOH	quartz	7·5	0·034	8	9·5		14		13	5		
t-BuOH	quartz	5·5[h]	0·034	10·5		18						

[a] Characterized as the methyl ester
[b] Photolysis of solid **1**, + unidentified polar products
[c] An attempt was made to identify all minor products
[d] CO_2 determined as $BaCO_3$ (97%) and McCHO as the 2,4-DNPH
[e] Under N_2
[f] Degassed
[g] — unidentified products (total 6%)
[h] Incomplete reaction, no other products detected

In addition it was shown that the yield of glycol **3** obtained by photolysis of **1** (MeOH, pyrex) is dependent on the initial concentration of **1**:

Concentration of **1** (moles/l of MeOH)	0·03	0·04	0·08	0·12	0·16
Yield of **3** (%)	10	36	44	56	60

Determination of structures

Compounds **2**[6], **5**[7] and **7**[6] are known: their m.p's, m.m.p's and spectra (IR, NMR, UV, mass) are identical with those of authentic samples. The glycol **3**, a white solid which precipitates from solution as it is produced, is insoluble in all the usual organic solvents, but readily soluble in mineral acids. IR and UV spectra indicate the presence of a pyridine nucleus as well as hydroxyl and ester groups. Cooling a solution of **3**

in HCl or HBr gives the hydrochloride or hydrobromide. Neutralization of these solutions causes unchanged **3** to precipitate. The NMR spectrum of crude **3** in 6N DCl compared to the spectrum of the hydrochloride suggests that the photoproduct is actually a mixture of two diastereoisomers one of which is the major product. This is evident from the duplication of peaks or shoulders on peaks.

The mass spectrum of the glycol **3** does not show a molecular ion (m/e 416) but a significant peak at m/e 417 (M + 1). As the ion source pressure is lowered m/e 417 disappears without the appearance of m/e 416. The base peak remains m/e 209 (M/2 + 1) which corresponds to the breaking of the glycol C—C bond accompanied by transfer of a hydrogen atom to the charged fragment. This is in accord with the proposed decomposition of aromatic glycols[8] as well as with our deuterium labelling experiments. In addition, the mass spectrum of the known 1,2-bis (3-pyridyl)-ethane-1,2 diol[9] is entirely analogous, presenting an (M + 1)$^+$ peak but no molecular ion, and fragmentation with hydrogen atom transfer.

Spectral data of several derivatives of **3**, including the diacetate, and bis-O-trimethylsilyl compounds are entirely in agreement with this structure. Proof of the structure **3** was obtained by quantitative periodate oxidation of **3** to **4** and then direct conversion of **4** (treatment with NaCN/MnO$_2$ in EtOH/AcOH)[10] to the known diester **2**.

R = COOEt

3   **4**   **2**
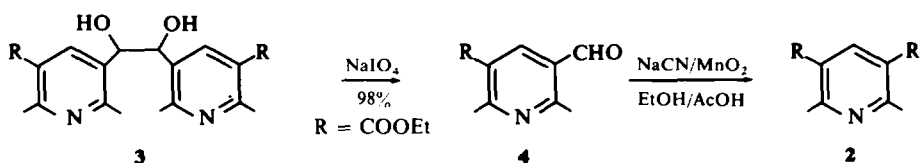
The aldehyde **4** was detected in the mixture from incomplete photolysis of **1** (MeOH, pyrex) by treatment with hydroxylamine and isolation of the oxime. Under different conditions (t-BuOH, quartz) the free aldehyde **4** could be isolated in significant yield. It was characterized by its spectral properties (IR, UV, NMR, mass) and those of its oxime. In addition it is obtained by oxidation of the glycol **3** and, as seen above, can be converted to the known diester **2**.

The diketone **6** was identified on the basis of its spectra; the structure was confirmed in two ways: hydrogenation of **6** gave glycol **3** and oxidation of **6** with alkaline H$_2$O$_2$[11] gave the diacid characterized as the methyl diester **12**.

6

(i) H$_2$O$_2$-OH$^\ominus$

(ii) H$^+$

(iii) CH$_2$N$_2$

3

12
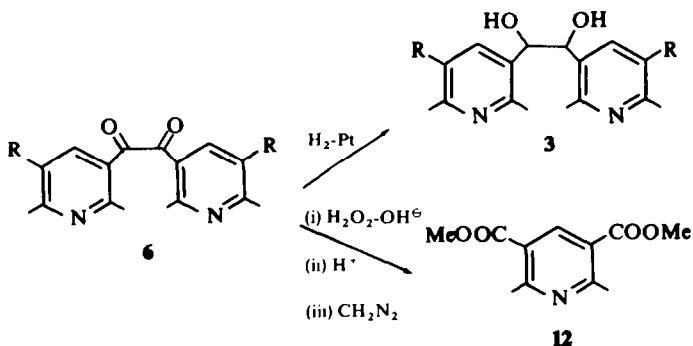
The new dihydropyridine **8** is an unstable yellow oil which when left in air for 2 days is oxidized to **2**. Its spectral properties permit the unequivocal assignment of structure **8**. In particular its UV spectrum is very characteristic of 1,2-dihydropyridines. Moreover, it has been converted (NaH/ClCO$_2$Et) to the relatively stable N-carbethoxyderivative **13**.[5]
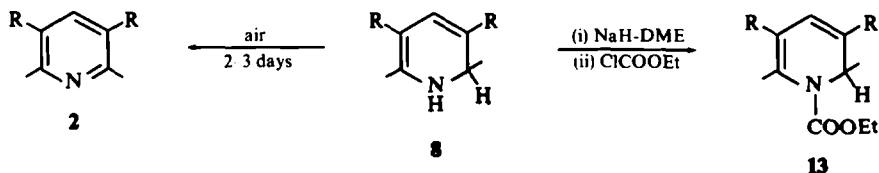

DISCUSSION

It is evident that, with EtOH or MeOH as solvent, the major photolysis product **3** arises *via* a secondary photochemical reaction of the primary product **4**. Such "pinacolic" photoreductions are well known for a number of aromatic ketones and aldehydes and yields are often very high.[12] We have verified that under the conditions of photolysis of **1** (MeOH, pyrex for example) **4** is converted cleanly and rapidly to glycol **3**. In these reactions the solvent alcohol is itself oxidized. We were thus able to characterize acetaldehyde formation during photolysis in EtOH by trapping it in a flow of N$_2$ and conversion to its 2,4-DNPH derivative. However, we were never able to detect formaldehyde when MeOH was used as solvent.

In the main photochemical process, the formation of the aldehyde **4** from **1**, the presence of a free carboxyl group is necessary; both the sodium salt and methyl ester of **1** are stable to photolysis. It was possible to exclude, as possible intermediates, the compounds **2, 7** and **11**.
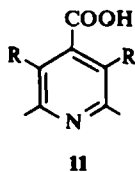
Photolysis of **7**, in MeOH or MeOH/AcOH solution, gave **2** as major product, a mixture of dimers, readily identified by their NMR and mass spectra. The pyridine **2** was stable to photolysis (pyrex) even in the presence of acid or of the methyl ester of **1**. Photolysis of **2** in quartz has been studied[4] and shown to give products of solvent addition and of photoreduction which, apart from the dihydropyridine **7**, are different from the products of photolysis of **1**. Acid **11** on photolysis (MeOH, pyrex) led to the formation of **2** and two other unidentified products which are however different from the products of photolysis of **1**. These results obviate mechanisms in which the first step is either a dehydrogenation (**1** → **11**) or a simple photodecarboxylation (**1** → **7**).[14]

When the photolysis of 1 is carried out in MeOD, the aldehyde formed contains one atom of deuterium, localized exclusively in the aldehyde group (mass spectrum); this was confirmed by oxidation to the diester 12 which contained no deuterium (mass spectrum).
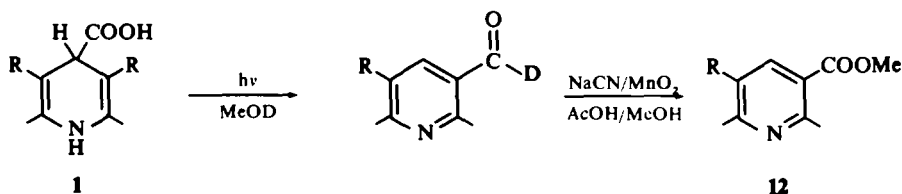
We have also verified that a similar photoreaction,[1] when carried out in t-BuOD leads to deuterium incorporation in the side chain:
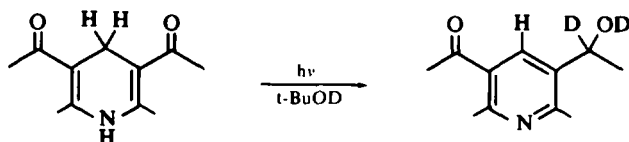
These labelling experiments exclude a direct migration of hydrogen from the 4-position to the ketone or ester carbonyl of the side chain, which would require the absence of deuterium in the aldehyde formed.

That conversion 1 → 4 is dependent on the presence of the carboxylic acid group implies that this group allows the stabilization, by protonation or hydrogen bonding, of a polar excited state, or even its direct participation in a concerted mechanism involving the elimination of CO_2.
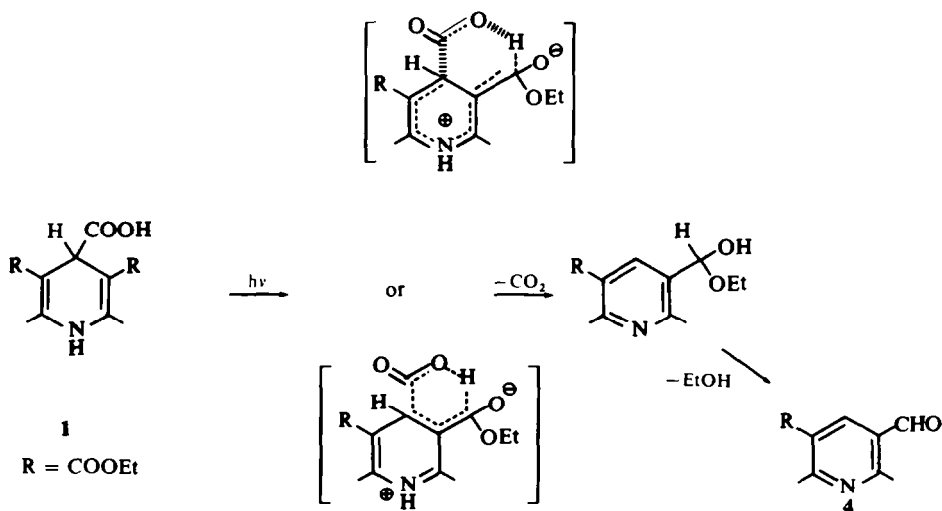
The aldehyde **4** itself does not accumulate in MeOH or EtOH where reductive-dimerization to the glycol **3** is rapid in comparison to its formation, and thus is only present in trace amounts.

The alcohol **5**, a minor product from photolysis of **1** in pyrex becomes a more important product when a quartz filter replaces pyrex. This product could come from photoreduction of **4** in competition with glycol formation, the former reaction being favoured by shorter wavelengths.

In contrast to results of photolysis of **1** in MeOH or EtOH as solvent, photolysis in t-BuOH or dioxane leads to lower yields of the glycol **3** and to a new product, the diketone **6**. This would seem to indicate inhibition of the reductive dimerization of the aldehyde **4**. It is known that benzaldehyde on irradiation gives benzoin.[15] This suggests in the present case, the formation of a ketol or ketolic radical which leads *via* a redox reaction to the diketone **6** and the glycol **3**.

The only notable difference on replacing the pyrex filter with quartz for photolysis is the appearance of the isomeric dihydropyridines **7** and **8**:

Photolysis of the pyridine **2** in alcohol solution, in quartz, has been shown to give the 1,4-dihydropyridine **7** in good yield[4] and no 1,2-dihydropyridine is mentioned. Since this product could easily escape detection due to its instability, we looked for the appearance of **8** during the photolysis of the diester **2** (quartz, MeOH), but no trace could be detected; under the same conditions, acid **1** gives a 13% yield of **8**.

The formation of the 1,4-dihydropyridine **7** from the photodecarboxylation of **1** and the photolysis of the pyridine **2** can be explained on the basis of a common intermediate, the radical *a*.
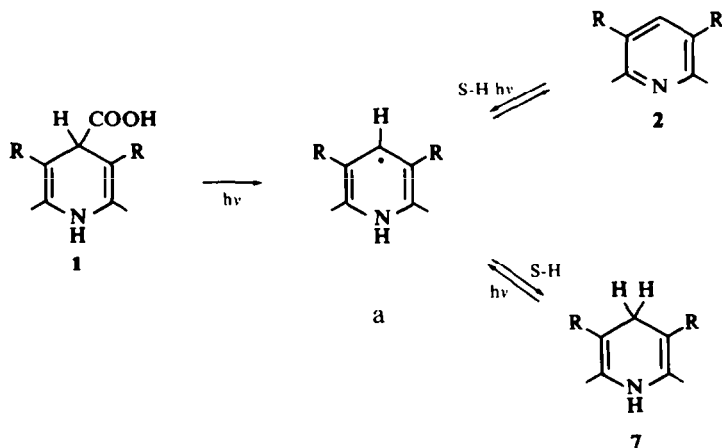
However, this does not explain the formation of the 1,2-dihydropyridine **8**, which could come from a concerted decarboxylation involving a double bond migration.
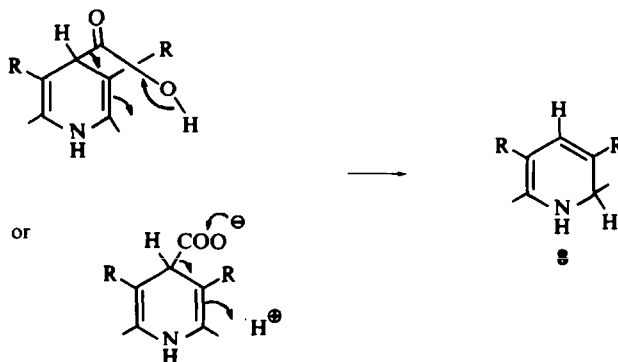
The radical *a* may reduce by hydrogen transfer the intermediate formed during the reductive photodimerization of the aldehyde **4** to the glycol **3**; this would explain the small amount of oxidized solvent and the appearance of the pyridine **2** as a major product.

CONCLUSION

The reduction of an ester to an aldehyde group by a dihydropyridine system occurs with participation of a proton from the solvent. This is in contrast to other examples where the dihydropyridine system behaves as a source of hydride ion in many redox reactions.[16] Here the dihydropyridine ring is acting as electron-donor.[5b]

EXPERIMENTAL

Nmr spectra were obtained on a Varian A-60 spectrometer using TMS (δ = 0·0 ppm) as internal standard. Ir spectra were obtained on a Beckman IR-8 spectrophotometer. Mass spectra was measured on a Thomson–Houston THN 208 spectrometer, by Dr. G. Teller and Mr. R. Hueber whose assistance is hereby acknowledged. The irradiations were performed with a lamp HPK Philipps 125 w.

Photolysis of 1 *in the solid state.* Acid 1 (1·0 g) was spread over the bottom of a pyrex dish floated in a water bath maintained at 18°. The solid was irradiated for 4 days with a Mazda MAF 125 w Lamp, then triturated with Et$_2$O and filtered from residual 1 (20 mg). The ether solution was evaporated to dryness and the residue (730 mg) taken up in AcOEt and chromatographed on a column of silicagel (25 g, hexane). Elution with hexane–AcOEt 4–1 furnished, on evaporation, a white crystalline solid (644 mg) identified as 2. Further elution (AcOEt, MeOH) gave mixtures of 2 with 3 other more polar products. None of these correspond to 7.

Photolysis of the sodium salt of 1. NaOH aq was added dropwise to a suspension of 1 (1·0 g) in water (35 ml) until all the solid dissolved. This solution was diluted with 95% EtOH (150 ml) and irradiated for 12 h under N$_2$. No CO$_2$ evolution was detected (Ba(OH)$_2$ solution). TLC examination during the course of the irradiation showed only starting material.

Photolysis of the methyl ester 1. Ester **5a** (1·0 g) in 95% EtOH (150 ml) was irradiated under N$_2$ for 17 h and unchanged starting material recovered quantitatively.

Photolysis of 1 *in ethanol (Pyrex).* A solution of 1 (2·0 g, 6·7 mmoles) in 95% EtOH (150 ml) was irradiated. Evolved gases were swept with a stream of N$_2$ through an aqueous solution of Ba(OH)$_2$. After 24 h irradiation it was found that 6·5 mmoles of BaCO$_3$ had been produced. Photolysis was stopped and the white

precipitate of the glycol 3 filtered from the EtOH solution and EtOH washed (500 mg: 36%). The filtrate and washings were combined, and the solvent removed. The residue was taken up in Et_2O and chromato-graphed on silicagel (20 g: pet–ether). Elution with pet. ether–ether 4–1 gave a white solid, 71–72° identified as the pyridine 2. The above experiment was repeated replacing the $Ba(OH)_2$ solution with a solution of 2,4-dinitro-phenylhydrazine. At the end of 24 h photolysis orange needles (35 mg) of acetaldehyde 2,4-DNP derivative were filtered and identified with authentic material. When MeOH was used as solvent the 2,4-DPNH derivative of formaldehyde was not found. Attempts to trap formaldehyde as the dimedone derivative were similarly unsuccessful.

Photolysis of 1 *in methanol (Pyrex).* Similar results were obtained. The yield of the glycol 3 was found to depend on the initial concentration of 1 (see above).

Characterization of aldehyde 4 *(MeOH–Pyrex).* A 0·034 N solution of 1 in MeOH was irradiated to approximately 80% consumption of starting material. The solution was filtered and the filtrate taken to dryness. The residue was triturated with ether and filtered to remove unreacted 1. The filtrate was evapor-ated and taken up in EtOH. Hydroxylamine hydrochloride was added and the pH adjusted to 9 with aq. NaOH. The solution was refluxed for 2 h, concentrated to half its volume, diluted with water and cooled. Small crystals were obtained which were purified to m.p. 206–208° by vacuum sublimation, and identified with the oxime of the aldehyde 4.

Identification of minor products from photolysis in methanol (Pyrex). A solution of 1 (98·3 mg) in MeOH (5·0 ml) was degassed by 3 freeze–thaw cycles and sealed in a pyrex tube which was then irradiated for 6 h. The tube contents were filtered to remove insoluble glycol 3 (38 mg). The filtrate was divided into 2 tubes. One was treated with CH_2N_2 to esterify any acids present. Analysis of these two solutions by GLC on three different columns led to the detection of 2, 4, 5, 9 and 10 (only for CH_2N_2 treated solution). The two fractions were combined and solvent removed. The residue was chromatographed on silicagel (2 g, hexane). Elution with hexane–AcOEt 7–3 gave 2 (34 mg). The results of GLC analysis could be estimated from the peaks areas (relative to 2): table.

Photolysis of 1 *in t-BuOH solution (Pyrex).* After irradiation of 1 as a 0·03 M solution in t-BuOH at 40° (CO_2 quantitatively evolved) and filtration of the glycol, the products were chromatographed on silicagel. The diketone 10 was eluted (below) with hexane–AcOEt 1–1. For the other products see table.

Photolysis of 1 *in dioxane (Pyrex).* A solution of 1 (5·0 g) in dioxane (200 ml), freshly distilled from LAH, was irradiated under N_2 for 24 h. The solution was filtered to remove glycol 3 (200 mg). The solvent was removed and the residue taken up in AcOEt and chromatographed on silicagel (200 g, hexane). Elution with hexane–AcOEt 9–1 gave 1·130 g of 2 contaminated with a small amount of aldehyde 4 (GLC). Elution with hexane–AcOEt 4–1 gave a yellow solid (540 mg) characterized as diketone 6. Elution with hexane–AcOEt 3–1 gave a further 40 mg of 6 contaminated with small amounts of the alcohol 5. Elution with MeOH gave 1·8 g of an intractable gum.

Identification of minor products from dioxane (Pyrex). 1 (84 mg) was dissolved in dioxane (5 ml), freshly distilled from LAH. The solution was degassed by 3-freeze–thaw cycles and irradiated for 64 h, filtered from a small amount of glycol 3 (6 mg) and the filtrate divided in two portions. One of which was treated with CH_2N_2. GLC analysis of the sample showed the presence of 2, 4, 12 (for CH_2N_2 treated solution), 6 and two unidentified products. The two solutions were combined and the solvent removed. The residue was chromatographed on silicagel (4 g, hexane). Elution with hexane–AcOEt 4–1 gave pure 2 (24 mg). The yields of the minor products were obtained from the GLC data: see Table.

Characterization of glycol 3. The white solid melted at 260–263° without decomposition and was com-pletely insoluble in all usual solvents (slightly in hot AcOH). It dissolved easily in dilute mineral acids and was precipitated from this solution on neutralizing with NaOH. The precipitated material had an identical IR spectrum (KBr) with the spectrum of the original material (i.e. 3140 cm^{-1} (OH very broad), 1730 cm^{-1} (C=O, strong)). Separation of diastereoisomers: the photoproduct (2·5 g) was dissolved in 20% HCl (30 ml) and cooled to 0°. White crystalline hydrochloride (1·6 g: 64%) m.p. 268–269°, was obtained. Similarly a hydrobromide was obtained, m.p. 228°.

NMR of the hydrochloride: (6N DCl) δ = 8·96 (s 2H, aromatic protons), 5·31 (s 2H, glycol), 4·48 (q 4H, ester CH_2), 3·07 (s 6H, Me), 2·95 (s 6H, Me), 1·43 (t 6H, ester Me). The mother liquors from the hydrochloride were made basic with NaOH, and a spectrum of the precipitated material recorded in 6N DCl: δ = 8·96 and 9·94 (aromatic protons), 5·48 and 5·31 (s, glycol H's), 4·48 and 4·43 (2 overlapping s, ester CH_2), 2·95 (s, Me), 3·07 (s Me), 1·43 and 1·38 (2 overlapping ts, ester Me). UV (as hydrochloride): λ_{max} 278 nm, ε 18·5 × 10^3 (Calc. for $C_{22}H_{28}N_2O_6$: C, 63·51: H, 6·78: N, 6·73. Found: C, 63·03: H, 7·11: N, 6·74%).

Acetylation of the glycol 3. Glycol 3 (130 mg) was heated in glacial AcOH (2·0 ml) at 80° with Ac_2O

(0·5 ml) for 22 h. A diacetate m.p. 126–128° was obtained in 78% yield after crystallization from cyclohexane. A second crystallization from cyclohexane raised the m.p. to 128 131° IR: 1748, 1725 cm⁻¹ (both strong: acetate and ethyl ester) NMR (CDCl₃, TMS): δ = 7·98 (s 2H, aromatic protons), 6·30 (s 2H, glycol), 4·38 (q 4H, ester CH₂), 2·80 (s 6H, Me), 2·50 (s 6H, Me), 2·10 (s 6H, acetate), 1·38 (t 6H, ester Me) (Calc. for $C_{26}H_{32}N_2O_8$: C, 62·45; H, 6·45; N, 5·60. Found: C, 62·48; H, 6·51; N, 5·69%). Mass spectrum: base peak at 208, significant peaks at 500 (M⁺), 455, 293, 251, 250. Acetylation in hot pyridine/Ac₂O gave the same compound in lower yield.

Trimethylsilyl derivative of the glycol 3. The glycol 3 (100 mg) was stirred in pyridine (2 ml) containing (Me)₃SiCl (0·2 ml) and [(Me)₃Si]₂NH (0·4 ml) for 24 h at room temp. The mixture was diluted with CHCl₃ and filtered. The filtrate was washed with very dilute H₂SO₄ until the washings were neutral, then with water, dried and evaporated. The residue crystallized in very poor yield from pentane at − 10° and had m.p. 120–123° and a retention time of 24 min on a 3 m column of 5% SE 30 at 200°. with a carrier gas (N₂) flow rate of 20 ml/min. NMR (CCl₄): δ = 7·89 (s 2H, aromatic protons), 4·58 (s 2H, glycol), 4·19 (q 4H, ester CH₂), 2·58 (s 6H, Me), 2·37 (s 6H, Me), 1·24 (t 6H, ester Me), 0·40 (s 18H, TMS ether). This silylated material was stable in refluxing MeOH but quickly reverted to starting material in hot MeOH to which a few drops of H₂SO₄ had been added.

Oxydation of the glycol 3. The glycol 3 (152 mg) was dissolved in N H₂SO₄ (3 ml) and the pH of the solution adjusted to ∼ 3 by addition of aq. NaOH. A solution of NaIO₄ (86 mg) in water (2 ml) was added and the solution stirred for 30 min. at room temp. CHCl₃ extraction gave a colourless oil (150 mg) which on standing solidified to white crystals m.p. 53·5–55°; aldehyde 4 (yield 98%). NMR (CDCl₃): δ = 10·10 (s 1H, aldehyde), 8·45 (s 1H, aromatic proton), 4·28 (q 2H, ester CH₂), 2·72 (s 6H, 2 Me's), 1·30 (t 3H, ester Me). IR (KBr): 1715 and 1697 cm⁻¹ (ester and aldehyde C=O). Mass spectrum: M⁺ = 207 (93%), significant peaks at 192, 179, 178, 162 (base peak), 135, 134, 106. This aldehyde gave an oxime m.p. 208–210° after crystallization from aq. EtOH. (Calc. for $C_{11}H_{14}N_2O_4$: C, 59·45; H, 6·35; N, 12·60. Found: C, 59·70; H, 6·47; N, 12·60%). It also gave a dimedone derivative m.p. 125–127° (aq. EtOH).

Oxydation of aldehyde 4 *to ester* 2. The aldehyde 4 (150 mg) was dissolved in absolute EtOH (4 ml) containing NaCN (165 mg), AcOH (65 mg) and Merck active MnO₂ (1·3 g).[10] The mixture was stirred at room temp for 24 h filtered, and the residue washed with EtOH. The filtrate and washings were combined and evaporated. The residue was chromatographed on a column of silicagel (12 g, hexane) and eluted with hexane–AcOEt 7–3. The early fractions gave after evaporation a white crystalline solid (135 mg; 77%) identical to authentic 2.

Diketone 6. Yellow crystals recrystallized from cyclohexane and then from EtOH, m.p. 164–165°, raised to 165–165·5° after sublimation. NMR (CDCl₃): 8·52 (s 2H, aromatic proton), 4·38 (q 4H, ester CH₂), 2·91 (s 6H, Me), 2·87 (s, 6H, Me), 1·40 (s 6H, ester Me). IR (KBr): 1727 and 1666 cm⁻¹ (ester and α-diketone C=O). UV: λ_{max} 258 nm, ε: 13·2 × 10³. Mass spectrum: M⁺ 412, significant peaks at 384, 367, 206 (base peak, high resolution $C_{11}H_{12}NO_3$). (Calc. for $C_{22}H_{24}N_2O_6$: C, 64·13; H, 5·87; N, 6·80. Found: C, 64·12; H, 5·88; N, 6·98%).

Conversion of diketone 6 *to glycol* 3. The diketone 6 (84 mg) was dissolved in MeOH (5 ml) and AcOH (10 ml) containing 10% Pd (15 mg) and hydrogenated at atmospheric pressure. After rapid uptake of hydrogen (9·1 ml), N₂ was bubbled through the solution which was then filtered from the catalyst. Solvent was removed under reduced pressure and the residue taken up in 2N HCl. This solution was washed with CHCl₃. The aqueous solution was made basic with aq. NaOH and the white precipitate removed by filtration, washed with H₂O and dried *in vacuo*. An IR spectrum of this material was identical to that of glycol 3.

Correlation of diketone 6 *with diester* 12. The diketone 6 (18·5 mg) was dissolved in dioxane (1 ml). A solution of KOH (100 mg) in MeOH (1 ml) was added and the resulting solution heated at 50°. 30% H₂O₂ (0·6 ml) was added dropwise over 20 min. and the solution heated for a further 20 min. at 50°. The solution was cooled, washed with ether, neutralized and lyophilized. The residue was treated with an etheral solution of CH₂N₂. Filtration and evaporation of ether afforded 5 mg of a white crystalline material, characterized as 12.

Photolysis of aldehyde 4. A solution of aldehyde 4 (518 mg) in MeOH was irradiated for 3 h. The white solid was filtered and characterized as glycol 3 (115 mg; 22%). Examination of the filtrate showed only starting material.

Preparation of monoacid 10a. The pyridine diester 2 (10·0 g) was dissolved in 95% EtOH (200 ml) and heated to reflux. KOH (0·56 g) in 95% EtOH (100 ml) was added in portions over 2 h. The solution was refluxed for a further 3 h. Solvent was removed and the residue dissolved in water. The pH was adjusted

to 5 and this solution was ether extracted. Drying and evaporation gave 420 mg of the monoacid **10a** m.p. 134–136° (lit.[13] 131°).

Preparation of acid **11**. 2,6-dimethyl-3,5-dicarboethoxy-4-pyridine carboxylic acid benzyl ester **5** (5 g)[5] was hydrogenated in MeOH (50 ml) containing 10% Pd (0·5 g). The solution was filtered from catalyst and the solvent removed. The residue was triturated with 1% aq. KOH and filtered. The filtrate was washed with ether, the pH adjusted to 3 and the solution was cooled in ice. Filtration afforded 0·5 g of yellow crystals m.p. 191–192°. Acidification to pH 2 and cooling yielded another 1·0 g. The two batches were combined, dissolved on hot MeOH which was then diluted with 2 volumes of water. A slow crystallization yielded 600 mg of pale yellow crystals m.p. 196° sharp. (lit.,[17] 181°).

Photolysis of acid **1** *in MeOD*. A solution of **1** (49 mg) in MeOD (15 ml) was sealed in a pyrex tube and irradiated for 10 h. At the end of this time GLC analysis showed products **2** and **4** to be present in a ratio of approximately 1 : 10. The mass spectrum of each of these products (introduction by GLC) showed that the pyridine **2** did not contain deuterium but that **4** contained one deuterium atom. From the fragmentation pattern this appeared to be present exclusively in the aldehyde side chain. The deuterium containing aldehyde was separated by prep. GLC on 2 m 20% SE 30 on chromosorb W.5.2 mg of material m.p. 52–53° was then obtained. This material was dissolved in McOH (0·5 ml) containing NaCN (6 mg), AcOH (0·02 ml) and Merck active MnO₂,[10] and stirred at room temp. After 48 h reaction time GLC showed approximately 50% conversion of the starting aldehyde to diester **10b**. A mass spectrum of this diester (introduction by GLC) confirmed its structure (compared with the spectrum of authentic material from acid **10a** + CH₂N₂) and further showed that it did not contain any deuterium.

Photolysis of 3,5-*diacetyl-2,6-dimethyl-1,4-dihydropyridine in* t-*BuOD*. Repetition of Eisner's photolytic reaction[1] gave the corresponding alcohol containing 1 D as shown by the NMR spectrum in CDCl₃: all

$$\text{OD}$$

Me appear as singlets at $\delta = 2·73, 2·63, 2·58$ and $1·54$ ($-\overset{|}{\underset{|}{C}}-·CH_3$).

$$\text{D}$$

Photolysis of **1** *in MeOH (quartz)*. A solution of **1** (2·0 g) in McOH (200 ml) was irradiated under N₂ for 10 h. The solvent was reduced to 30 ml and the glycol **3** (184 mg, washed with MeOH) filtered. The filtrate and washings were combined and the solvent removed. The residue was chromatographed on silicagel (50 g, CHCl₃). Elution with CHCl₃ gave a mixture (450 mg) of **2**, **7** and **8**. Further elution using CHCl₃– AcOEt yielded a yellow gum (50 mg) followed by fractions containing alcohol **5** (100 mg). For yields see table.

Photolysis of **1** *in EtOH (quartz)*. A solution of **1** (2·0 g) in 95% EtOH (200 ml) was irradiated under N₂ for 7·5 h. The solvent was removed, the residue taken up in MeOH (50 ml), the glycol **3** (130 mg) filtered. Evaporation of filtrate to 10 ml and cooling gave yellow crystals of the dihydropyridine **7** (92 mg) identified with authentic material. The filtrate was evaporated and the residue chromatographed on a column of silicagel (40 g, pet. ether). Elution with mixtures of pet. ether–AcOEt 4–1 to pure AcOEt gave successively the pyridine **2** (136 mg), the dihydropyridine **7** (129 mg, total 221 mg), the dihydropyridine **8** (80 mg, containing traces of **7**) followed by mixtures (610 mg), some of which crystallized, after evaporation of the solvent. From this material, recrystallization in ether gave the alcohol **5** (202 mg) as a white solid identified with an authentic sample.[7]

Photolysis of **1** *in tBuOH (quartz)*. A solution of **1** (2·0 g) in t-BuOH (200 ml) was irradiated under N₂ at 35–40° for 5·5 h (incomplete reaction). The solvent was removed and the residue triturated with CHCl₃.

The remaining crystals (300 mg) were identified as **1**. The filtrate was chromatographed on a column of silicagel (40 g, CHCl₃). Elution with CHCl₃ gave pyridine **2** (98 mg) followed by fractions (266 mg) containing **2** and aldehyde **4** in a 20:80 ratio (yield respectively 10·5 and 18%). Investigation of more polar photoproducts was not attempted.

Isolation of the dihydropyridine **8**. **1** was irradiated as a McOH solution as above (N₂, quartz vessel) but, after filtering off glycol **3** and removing solvent, the crude residue was chromatographed using thick layer plates (Merck silicagel). The plates were eluted with CHCl₃ (3 times). The bright yellow band corresponding to compound **8** was recovered and eluted with AcOEt. Evaporation of the solvent gave an unstable yellow oil (65 mg). NMR (CDCl₃): $\delta = 7·72$ (s 1H, H₄), 6·15 (broad 1H, NH), 4·60 (1H, H₂), 4·20 and 4·22 (2 overlapping quartets 4H, ester CH₂), 2·36 (s 3H, methyl-6), 1·28 (t 6H, ester Me), 1·15 (d 3H, methyl-2, $J = 7$ Hz). UV: $\lambda_{max} = 375$ nm $\varepsilon = 5850$; $\lambda_{max} = 285$ nm $\varepsilon = 14300$.

Preparation of dihydropyridine **13**. A solution of **8** (60 mg) in anhydrous 1,2-dimethoxyethane (6 ml, freshly eluted from alumina) was treated, under N₂, with NaH (50 mg of a 50% suspension in oil). The

mixture was stirred for 15 min (red solution) and treated with ethyl chloroformate (0·2 ml), then further stirred for 5 min. A few drops of sat NH_4Cl aq. were added, followed by CH_2Cl_2 (20 ml). The solution was filtered. dried and the solvent removed. The residue was purified on prep silicagel TLC (elution with $CHCl_3$ 3 times). The product was recovered with AcOEt as a pale yellow oil and purified by vacuum micro-distillation to yield 42 mg of 13 (the product darkened slowly, even at 0°). NMR ($CDCl_3$): $\delta = 7·43$ (s 1H, H_4). 5·34 (q 1H, H_2), 4·26 and 4·28 (two overlapping quartets 6H, ester CH_2), 2·60 (s 3H, Me 6), 1·32 and 1·34 (two overlapping triplets 9H, ester Me), 1·14 (d 3H, Me 2, $J = 7$ Hz). UV $\lambda_{max} = 339$ nm, $\varepsilon = 4750$; $\lambda_{max} = 235$ nm, $\varepsilon = 10,000$. Mass spectrum: $M^+ = 325$ (20%), significant peaks at 310 (base peak, M-CH_3). 280, 266, 238, 210, 182. (Calc. for $C_{16}H_{23}NO_6$: C, 59·21: H, 7·53: N, 4·38. Found: C, 58·89: H, 7·39: N, 4·26%).

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