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THE PHOTOCHEMISTRY OF 3,5-DISUBSTITUTED 1,4-DIHYDROPYRIDINES*

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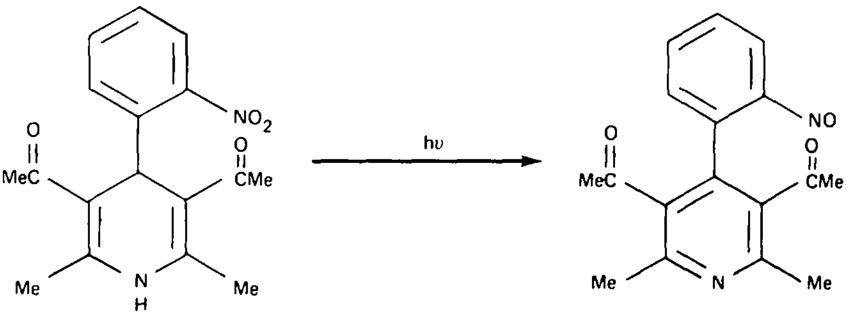
Abstract—On irradiation, 1,4-dihydropyridines have been shown to undergo three types of reaction: disproportionation, isomerization and dimerization. The presence of 2,6-substituents inhibits these reactions except in the case of **3a** which undergoes disproportionation. The diester **10** and diketone **11** yield mixtures of the corresponding 1,2-isomers and photodimers. The structure and stereochemistry of the dimers derived from **10** have been established by X-ray and NMR methods to be head-to-tail *anti*, **17**, and head-to-tail *syn*, **16**. The latter compound cyclizes to the cage isomer **15** upon further irradiation.

ABELSON *et al.*[1] have examined the photoreactivity of reduced nicotinamide-adenine dinucleotide (NADH) and have speculated as to the biological significance of the photoproducts. There are few reports, however, of the photochemical reactions associated with the chromophore, 1,4-dihydropyridine, present in NADH. Berson and Brown[2] have shown that on irradiation, the 1,4-dihydropyridine **1** underwent disproportionation with loss of the elements of water to **2**.



1 2

We find that the photoreactivity of 1,4-dihydropyridines is remarkably sensitive to substituent effects. In particular, the presence of 2,6-Me substituents inhibits photolysis in all but one case (*vide infra*) under the conditions studied (t-butanol, medium pressure mercury lamp, N$_2$ atmosphere). Thus, irradiation of **3b–c** and **4a–c** resulted in the recovery of unchanged starting material. This lack of reactivity is possibly due to steric factors.

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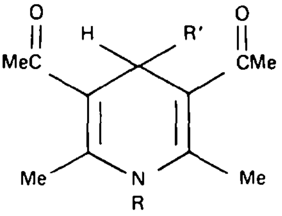

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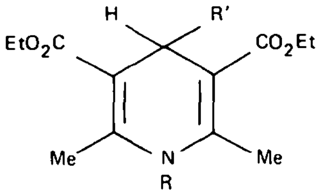
a, R = R' = H
b, R = H,R' = Me
c, R = Me, R' = H



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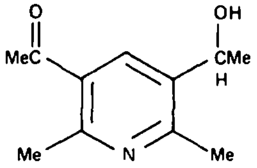
a, R = R' = H
b, R = H,R' = Me
c, R = R' = Me



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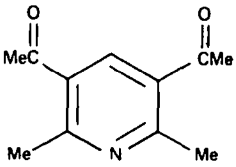

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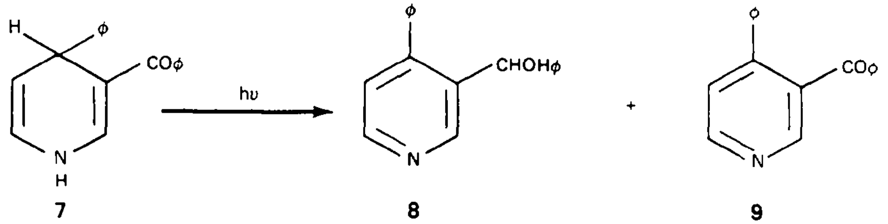
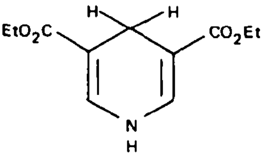
Irradiation of **3a**, however, afforded a single isomeric photoproduct. The NMR spectrum of this product showed a quartet centered at δ 5·13 (J = 6 Hz) and a doublet at δ 1·50 (J = 6 Hz) (CH-CH_3), a singlet at δ 8·12 (4-H) and three types of Me groups (δ 2·53, 2·58 and 2·68) suggesting the structure **5**. The IR and UV spectra (Experimental) were consistent with this structure. Chromic acid oxidation of the photoproduct yielded the known[3] diacetyl pyridine **6** thus completing the structure proof. It is interesting to note that no photooxidized material **6** was obtained during the irradiation. This is in contrast to the recent report[4] of the photolysis of **7** where both the disproportionation product **8** and photooxidation product **9** were obtained.

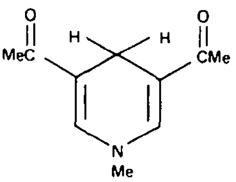
A number of dihydropyridines analogous to **3** and **4** but unsubstituted in the 2,6-positions were found to undergo photolytic reactions. Of these, the diester **10** and



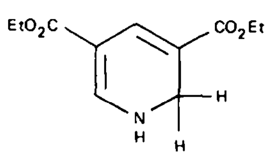
7 **8** **9**



10



11



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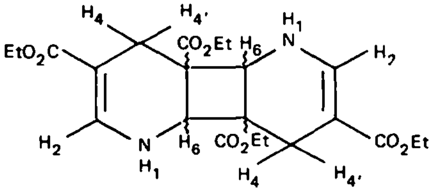
diketone **11** were selected for detailed study. Photolysis of **10** for 3 hr afforded a colorless product, m.p. 228°, which was isolated by crystallization. A minor unstable reaction product was formed in low yield and isolated by chromatography. The latter was shown to be the 1,2-dihydropyridine **12** by comparison with an authentic sample.[5] This represents the first recorded instance of the isomerization of a 1,4-dihydropyridine into the corresponding 1,2-dihydro derivative, although the photoisomerizations of 4-benzyl-2,4,6-triphenyl-4*H*-pyran and -thiapyran to 2-benzyl-2,4,6-triphenyl-2*H*-pyran and -thiapyran, respectively, have been described.[6]



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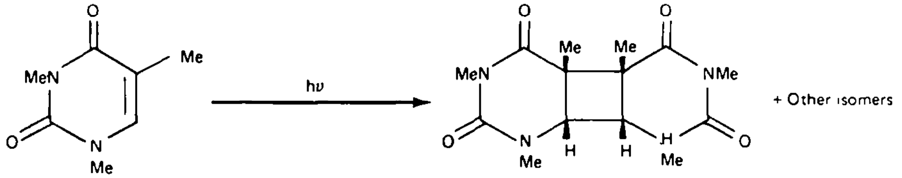
The UV spectrum of the major photoproduct (m.p. 228°), formed in approximately 60% yield, has λ_{max} at 277 nm (ε 40,000) indicating the presence of a 3-aminocrotonate chromophore.[7] Elemental analysis and mol wt determinations indicated a dimeric structure with the same formula as the starting material. The NMR spectrum of the compound, henceforth referred to as dimer I (Fig. 1, Table 1), shows an olefinic proton, two aliphatic protons, two sets of Et groups as well as hydrogen on a carbon bearing a nitrogen. These spectroscopic properties are most reasonably accounted for by a cyclobutane photodimer **13** (or its head-to-head isomer) analogous to those obtained in the irradiation of dimethylthymine **14**.[8]



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Irradiation of **10** in the solid state produced an isomeric dimer, m.p. 200° (dimer II) in high yield. Its UV and NMR (Fig. 1, Table 1) spectra showed that it, too, had a structure such as **13** or its head-to-head isomer. It was found to be accompanied by small amounts of dimer I as shown by TLC and was also produced in low yield on irradiation of **10** in solution. The mass spectra of the two dimers showed a weak parent ion of *M*/*e* 450 and the fragmentation pattern was essentially identical with that of the monomer **10**. On vacuum sublimation at 220° dimer II was partially converted into **10**.

When a solution of **10** was irradiated for 10 hr, a third photodimer (dimer III) was isolated, together with dimer I and diethyl pyridine-3,5-dicarboxylate. In contrast to the other dimers, dimer III did not absorb in the UV and its NMR spectrum (Fig. 1, Table 1) no longer showed the olefinic absorption present in dimers I and II. The UV and NMR spectra, therefore, suggest a cage dimer similar to those obtained by

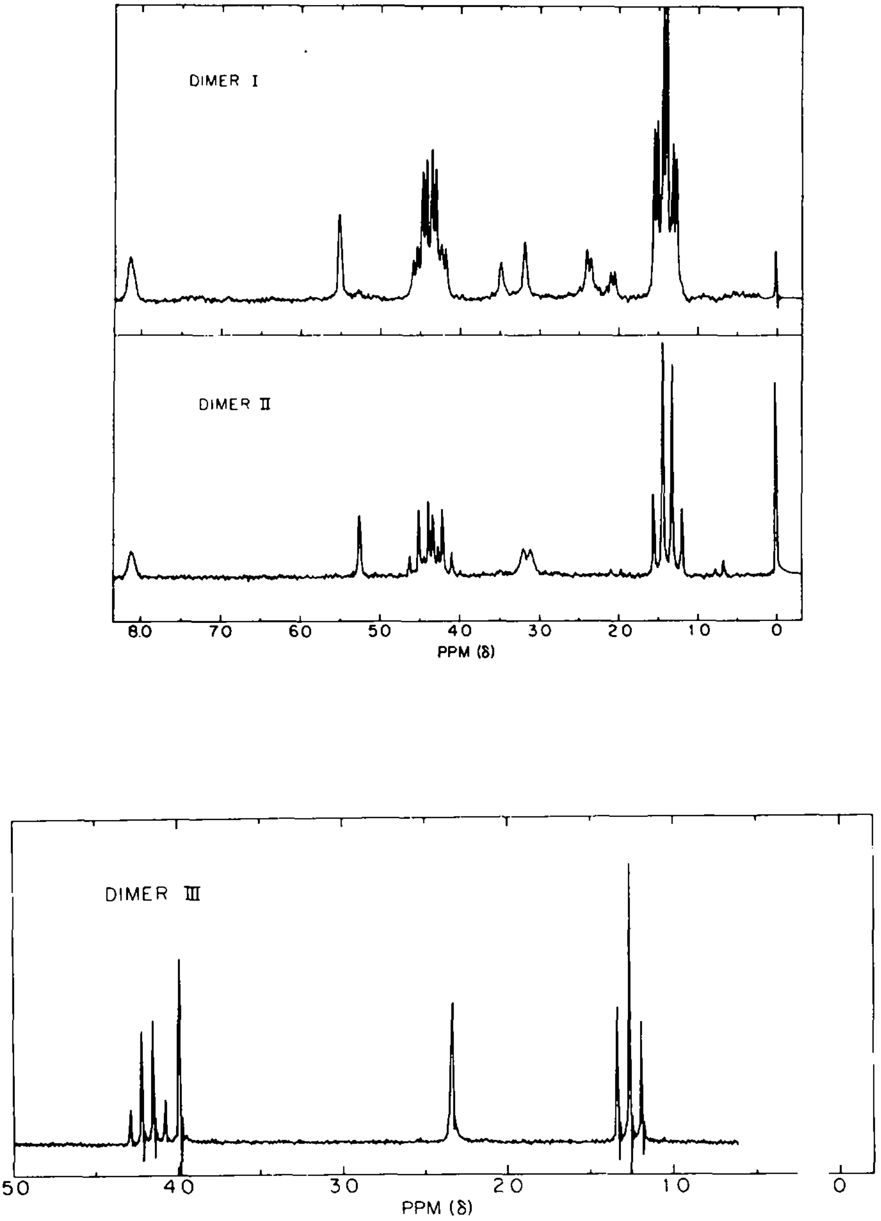
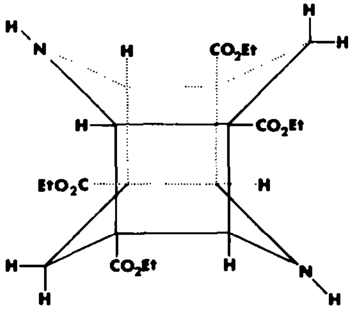


FIG. 1 NMR spectra of Dimers I, II (TFAA) and dimer III ($CDCl_3$).

the irradiation of alkyl benzoquinones[9] and γ-pyrones.[10] In order to determine whether dimer I was a direct precursor of dimer III it was irradiated under the same conditions when it was smoothly converted into dimer III. Furthermore, chromatography of dimer III on alumina resulted in its conversion to dimer I. These observations are most reasonably accounted for if dimer I has a *syn* stereochemistry about the cyclobutane ring.

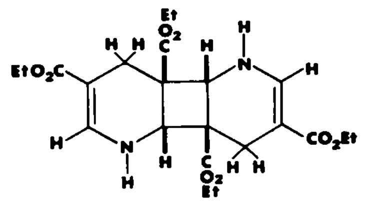
The mode of dimerization, h-h or h-t, of similar compounds has been established by NMR examination of the C^{13}-H satellite peaks of cyclobutane protons.[11] However, in the 1,4-dihydropyridine dimers I and II the cyclobutane proton absorption (in $CDCl_3$) is obscured by the methylene protons of the ester group although addition of C_6D_6 permitted its identification. A more complete separation of the cyclobutane proton was achieved by using trifluoroacetic anhydride as solvent, but examination of the C^{13}-H satellite in this system did not lead to unequivocal results. The cyclobutane protons in dimer III were well separated from the ester methylene protons in $CDCl_3$ and examination of its high field satellite ($J_{C^{13}-H}$ 145 ± 2 Hz) showed it to be a broad (3–4 Hz) single band. Since the cage structure requires the two protons on the cyclobutane ring to be *cis* and since vicinal *cis* coupling is generally 6–8 Hz[12] a broadened singlet indicates that the dimer has been formed by head-to-tail fusion. The broadening of the satellite results from the combined effects of quadrupole broadening by the N atom, 1,3 coupling across the cyclobutane ring and long range coupling to the 4- and 4′- protons. The structure of dimer III is, therefore, as shown in **15**.



15

The structural assignment of **15** for dimer III was confirmed by an X-ray determination of the space group. The space group and approximate cell dimensions were determined from precession photographs. Systematic absences indicated space group $P2_1/n$. Diffraction angles were measured later with a diffractometer and a least squares refinement gave the following cell parameters (estimated errors in parentheses) $a = 14{\cdot}70\ (0{\cdot}01)$ Å, $b = 6{\cdot}176\ (0{\cdot}003)$ Å, $c = 13{\cdot}70\ (0{\cdot}01)$ Å, $\beta = 115{\cdot}25\ (0{\cdot}06)^\circ$. The calculated unit cell volume is 1125 $Å^3$. The measured density was 1·31 g/cc and the density, calculated on a basis of 2 molecules per unit cell, was 1·32 g/cc. No evidence of disorder scattering was apparent on the photographs and a nearly completed refinement of the crystal structure (conventional R-factor 11%) appears to confirm that the crystal is ordered (private communication, J. V. Silverton, Georgetown University). The presence of only two molecules in the unit cell requires them to be at special positions. Such a molecule is required to have a center of symmetry.

The only cage structure that satisfies this requirement is the h-t cage dimer **15**. Since dimer III and dimer I differ only with regard to the presence or absence of the second cyclobutane ring dimer I is the head-to-tail *syn* dimer **16**.[*]



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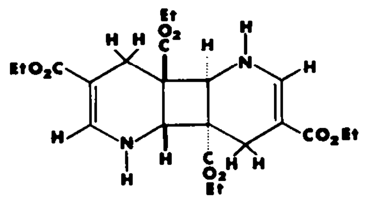

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Our inability to obtain an unequivocal answer to the mode of dimerization from the C^{13}-H satellite made the structure determination of dimer II considerably more difficult. Since dimer II did not form a cage dimer on further irradiation the stereochemistry about the cyclobutane ring was either *anti* or one of the six-four ring junctions was *trans*. The structure of dimer II was deduced from an X-ray determination of the space group in the following way. The space group was established from zero and upper level Weissenberg photographs as being triclinic with unit cell dimensions (estimated errors in parentheses) $a = 6{\cdot}37$ (0·05) Å, $b = 7{\cdot}38$ (0·05) Å, $c = 12{\cdot}97$ (0·05) Å, $\alpha = 107\ (1)^\circ$, $\beta = 101\ (1)^\circ$, $\gamma = 96\ (1)^\circ$. There is one molecule per unit cell ($d_{obs} = 1{\cdot}31$ g/cc, $d_{calc} = 1{\cdot}33$ g/cc, $V_{calc} = 562$ Å^3). The space group symmetry could either be $P\bar{1}$ or P1. In order to differentiate between these two groups the technique of Howells, Phillips and Rogers[13] was employed. In this procedure a graph of the fraction N(Z) of reflections whose intensities are equal to or less than a fraction Z of the local average intensity is made. Data for this plot were measured visually from Weissenberg photographs and corrected for the usual Lorentz and polarization factors. Data included in the N(Z) plot were limited to the range $0 < \sin^2 \theta/\lambda^2 < 0{\cdot}5$, as at higher Bragg angles many of the reflections were too weak to be measured reliably. To provide a reasonable statistical sample both the (0kl) and (1kl) intensities were included and the resultant values of N(Z) for 195 reflections were plotted (Fig. 2) along with the theoretical distributions for centrosymmetric and noncentrosymmetric space groups. The observed data agree well with the centrosymmetric curve indicating that the space group is $P\bar{1}$. Since there is only one molecule per unit cell,

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[*] The following IUPAC names have been kindly supplied by Dr. Loening of Chemical Abstracts Service:

16. Tetraethyl 1,5,8,8bβ-tetrahydrocyclobuta[1,2-*b*: 3,4-*b*′]dipyridine-3,4aβ,7,8aβ(4*H*, 4*b*β*H*) tetracarboxylate.
17. Tetraethyl 1,5,8,8*b*α-tetrahydrocyclobuta[1.2-*b*: 3.4-*b*′]dipyridine-3,4*a*α,7,8*a*β(4*H*,4*b*β*H*)tetracarboxylate where the α/β nomenclature is used as in steroids.
15. Tetraethyl 3,9-diazahexacyclo[$6.4.0.0^{2,7}.0^{4,11}.0^{5,10}$]dodecane-1,5,7,11-tetracarboxylate. However, for the sake of simplicity we have retained the trivial names.

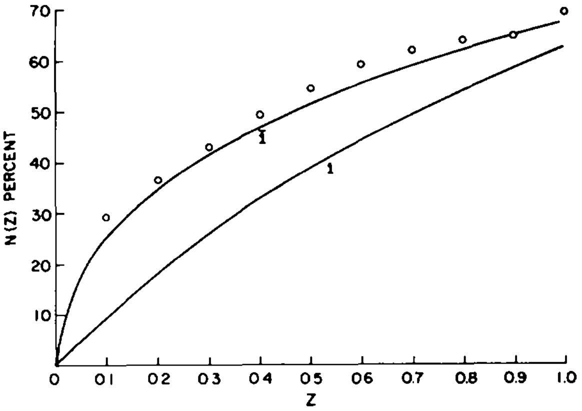
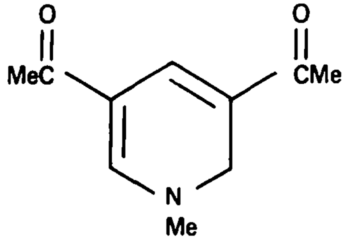


FIG. 2 Theoretical curves (—) and experimental data (o) distinguishing between $P\bar{1}$ and P1.

and as there is no indication that the crystal structure is disordered, it follows that the molecule has an inversion center. There are only two structures compatible with this requirement and both of these are h-t dimers. In the first, both ring junctions are *cis* and the molecule must be *anti*, and in the second both ring junctions must be *trans*. This second possibility is extremely unlikely since in order to form during the irradiation, the two molecules would have to be packed in this manner in the crystal. Furthermore, there are no examples of such strained di-*trans* fused six-four ring junctions. The most reasonable structure for dimer II is therefore **17**.



19

Irradiation of **11** similarly gave a photodimer **18** and the 1,2-dihydropyridine **19**. The structure of the latter was established from spectral data (Experimental). The UV and NMR (Fig. 3, Table 1) of **18** indicate a cyclobutane structure analogous to **13**. Unlike the ester dimers **16** and **17** the cyclobutane protons in **18** were coupled to the 4-protons as evidenced by double irradiation experiments. This difference may be due to the conformational restrictions imposed by the bulky N-Me groups as shown by an examination of molecular models. The 4′-protons were coupled to the olefinic protons as in the case of **16** and **17**. Examination of the C^{13}-H satellite of the cyclobutane in **18** did not give useful results nor did further irradiation of **18** lead to identifiable products. The detailed structure and stereochemistry of **18** thus remain in doubt.

TABLE 1. 100 M/Hz SPECTRA OF 1,4-DIHYDROPYRIDINE PHOTODIMERS

Compound	Solvent	2-H[e]	4,4′-H[e]	6-H[e]	Ester CH$_2$	Ester CH$_2$
Dimer I **16**	CDCl$_3$	7·68q $J_{2,1}$ = 6·0 Hz $J_{2,4'}$ = 1·0 Hz	2·74d,4-H 2·34q,4′-H $J_{4,4'}$ = 1·0 Hz	—[d]	4·19q J = 6·0 Hz	1·36t 1·38t
	CDCl$_3$-C$_6$D$_6$-D$_2$O	7·48d[a] $J_{2,4'}$ = 1·5 Hz	2·69(b),4-H 2·28q,4′-H $J_{4,4'}$ = 18·0 Hz	4·14s(b)	4·05q 4·09q J = 7·0 Hz	1·12t 1·18t
	TFAA[b]	8·12s(b)	3·31d,4-H 2·20q,4′-H $J_{4',2}$ = 3·0 Hz $J_{4,4'}$ = 18·0 Hz	5·51s(b)	4·36q 4·40q J = 7·0 Hz	1·36t 1·41t
Dimer II **17**	CDCl$_3$	7·56d $J_{2,1}$ = 6·0 Hz	2·84d,4-H 2·60d,4′-H $J_{4,4'}$ = 18·0 Hz	—[d]	4·21q 4·24q J = 7·0 Hz	1·30t
	CDCl$_3$-C$_6$D$_6$-D$_2$O	7·28s(b)	2·80d(b),4-H[c] 2·55d(b),4′-H $J_{4,4'}$ = 17·0 Hz	3·97s(b)	3·95q 4·09q J = 7·0 Hz	1·02t 1·14t
	TFAA	8·10s(b)	3·31d,4-H 2·99d,4′-H $J_{4,4'}$ = 18·0 Hz	5·24s	4·26q 4·44q J = 7·0 Hz	1·30t 1·42t
Dimer III **15**	CDCl$_3$	3·99s	2·33s	3·99s	4·19q J = 7·0 Hz	1·26t
					COCH$_3$ unsat. COCH$_3$ sat.	NCH$_3$
18	CDCl$_3$	7·47d[a] $J_{2,4'}$ = 1·6 Hz	2·51q,4-H 1·87q,4′-H $J_{4,4'}$ = 19·0 Hz	3·86d[a] $J_{6,4}$ = 1·0 Hz	2·20s 1·85s	3·17s

s = singlet, d = doublet, t = triplet, q = quartet, b = broad

[a] Double irradiation

[b] 60 M/Hz

[c] Both 4- and 4′-protons sharpen on irradiation of 2-H

[d] Obscured by ester methylene group.

[e] For numbering see 13.

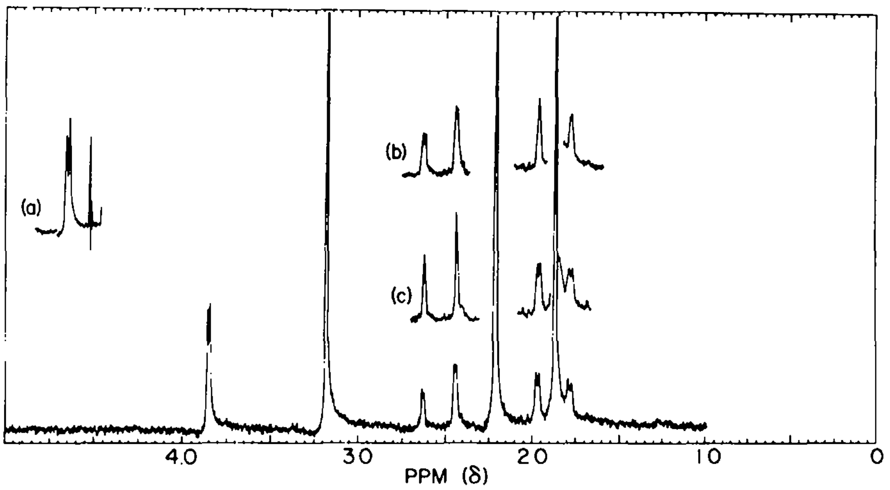


FIG. 3 NMR spectrum of **18** ($CDCl_3$)
(a) Olefinic proton and $CHCl_3$
(b) Irradiation at 3·86
(c) Irradiation at 7·47

EXPERIMENTAL

M.p's were determined on a Kofler block and are uncorrected. IR spectra were taken on Beckman IR-7 and Perkin–Elmer 137 spectrophotometers. UV absorption spectra were measured in EtOH soln with Cary 14 and Perkin–Elmer 202 spectrophotometers. The NMR spectra were obtained with Varian A-60 and HA100 spectrometers. TLC was carried out on commercial plates (Brinkman) of silica gel F-254 using as solvent hexane-EtOAc (1:1) (system A) or chloroform-acetone (7:3) (system B). Mass spectra were determined on an AEI MS9 instrument operating at 70 ev.

Photolysis of 3,5-*diacetyl*-1,4-*dihydro*-2,6-*dimethylpyridine* (**3a**).

The following procedure is typical for all the photolyses carried out in soln. A soln of **3a** (300 mg) in t-BuOH (180 ml), stirred with a stream of N_2, was irradiated with a 450 W Hanovia lamp through a Pyrex filter. The reaction, which was complete in about 4 hr, was monitored by TLC, system B (disappearance of 1,4-dihydropyridine). Evaporation of the solvent *in vacuo* yielded an oil, which was taken up in ether, the soln was filtered to remove a trace of fine ppt and the solvent removed. Crystallization of the residue from hexane afforded 3-*acetyl*-2,6-*dimethyl*-5α-*hydroxyethylpyridine* (**5**; 100 mg) which after recrystallization from hexane had m.p. 85–86°. (Found: C, 68·71; H, 7·70; N, 7·21. $C_{11}H_{15}NO_2$ requires: C, 68·37; H, 7·82; N, 7·25%); ν_{max} 3610 (OH) 1687 (conj. C═O) 1585 (C═C) cm^{-1}. λ_{max} 280, 240 nm (ε 4200, 6400).

Oxidation of 3-acetyl-2,6-dimethyl-5α-hydroxyethylpyridine (**5**).

To **5** (100 mg) in AcOH (1 ml) was added Jones reagent[14] (0·4 ml). After 45 min at room temp and 2 hr at 0°, MeOH and water were added. The soln was basified with NH_4OH, and extracted with ether. Evaporation of the etheral layer followed by crystallization from hexane afforded **6** (39 mg) which after recrystallization from hexane had m.p. 70–71°, undepressed on admixture with an authentic specimen; ν_{max} 1690 (conj. C═O), 1585 (C═C) cm^{-1}; π_{max} 282 (s), 277, 247 nm (ε 2500, 3450, 8000); NMR δ 2·63 (s, 2,6-CH_3) 2·80 (s, $COCH_3$) 8·25 (s, 4-H).

Photolysis of diethyl 1,4-*dihydropyridine*-3,5-*dicarboxylate*[15] (**10**).

(a) *In solution.* A soln of **10** (700 mg) in t-BuOH (180 ml) was irradiated for 2·5–3·5 hr as described. The reaction was monitored by TLC [system A]. The residue, after evaporation was treated with ether, and afforded a crude photodimer (420 mg; 60% yield) and mother liquor A. Recrystallization of the crude dimer from benzene or EtOAc afforded *dimer* I (**16**) (220 mg, 32%) m.p. 229°. (Found: C, 58·49; H, 6·80; N, 6·16;

M.W. by osmometry 447. $C_{22}H_{30}N_2O_8$ requires C, 58·65; H, 6·71; N, 6·22%; M. W. 450); ν_{max} 3452 (NH) 1721 (COOEt) cm^{-1}; λ_{max} 277 nm (ε 40,000).

The mother liquors from the crystallization of the crude dimer were evaporated to dryness and the residue dissolved in acetone. On cooling, crystals of dimer II (**17**) (see below), m.p. 190–200°, were obtained.

The mother liquors A were evaporated to dryness and chromatographed on silica gel using benzene-2% EtOAc as eluent. The 1,2-dihydropyridine **12** (5 mg) was isolated as a bright yellow solid which after crystallization from benzene-hexane had m.p. 73–79°, undepressed on admixture of an authentic sample,[5] m.p. 79–87°. The UV and IR spectra were identical.

(b) *In the solid state.* **10** (200 mg) was dissolved in ether and the soln allowed to evaporate with swirling inside a 1-l flask. The solid film was exposed to direct sunlight for 2 days, by which time the yellow color had disappeared. Crystallization from benzene afforded *dimer* II (**17**; 145 mg) which after two further crystallizations from benzene or EtOAc had m.p. 200–201° (Found: C, 58·70; H, 6·56; N, 6·07. M.W. by osmometry 445; $C_{22}H_{30}N_2O_8$ requires C, 58·65; H, 6·71; N, 6·22%; M. W. 450); λ_{max} 280 nm (41,900); ν_{max} 3460 (NH), 1725 (ester) cm^{-1}.

It was identical (mixed m.p., IR, TLC) with the sample of dimer II obtained by irradiation of **10** in soln (see above).

In another experiment, **10** (890 mg) was irradiated in a similar manner using electric light bulbs (~ 700 W). After 2 days the product was treated with ether affording dimer II (430 mg). The mother liquors were evaporated and irradiation continued for 3 days. On addition of ether dimer II (340 mg) was isolated. TLC (system A) showed that the second crop contained some dimer I.

Pyrolysis of dimer II. On heating dimer II at 220°/0·3 mm a yellow and a colorless sublimate were produced. The former was shown to be **10** and the latter starting material by TLC in system A.

Photolysis of diethyl 1,4-*dihydropyridine*-3,5-*dicarboxylate.*

Preparation of dimer III (**15**). A soln of **10** (1·0 g) in t-BuOH (200 ml), was irradiated for 10 hr as above. Evaporation of the solvent yielded a yellow gum which crystallized. Most of this crystalline material dissolved when triturated with a small amount of warm benzene. The insoluble material (60 mg), when recrystallized from benzene, was identical with **16**, m.p. and mixed m.p. 226–228°. Upon cooling, the benzene soln deposited needles (350 mg). Recrystallization from benzene-light petroleum afforded dimer III, **15**, m.p. 160–161°. (Found: C, 58·92; H, 6·77; N, 6·0%; M$^+$ (mass spec) 450. $C_{22}H_{30}N_2O_8$ requires: C, 58·65; H, 6·71; N, 6·22%; M. W. 450); ν_{max} 3300 (NH), 1730 (ester cm^{-1}).

Chromatography of the mother liquors from the above crystalline materials over silica gel afforded diethyl pyridine-3,5-dicarboxylate,[16] m.p. and mixed m.p. 48°.

Isomerization of dimer III to dimer I. Dimer III (100 mg) was dissolved in benzene and chromatographed over Woelm neutral alumina (Act. I; 10g). Benzene (3 × 100 ml) eluted dimer III (10 mg), m.p. and mixed m.p. 159–161°, and EtOAc (3 × 100 ml) eluted dimer I (70 mg) m.p. and mixed m.p. 215–228°, identical IR spectra.

Photoisomerization of Dimer I to Dimer III. Dimer I (100 mg) was dissolved in t-BuOH (100 ml), and irradiated as for **10** for 5 hr. Evaporation of the solvent *in vacuo* yielded a yellow gum, the NMR of which indicated the presence of dimer III in better than 90% yield. The remaining peaks corresponded with those of diethyl pyridine-3,5-dicarboxylate. The presence of dimer I or of the monomeric **10** could not be detected.

Photolysis of dimer II for extended periods of time led to the slow decomposition of dimer II and the gradual formation of diethyl pyridine-3,5-dicarboxylate.

Photolysis of 3,5-*diacetyl*-1,4-*dihydro*-1-*methylpyridine*[15] (**11**).

A soln of **11** (300 mg) in t-BuOH (180 ml) was irradiated for 1 hr as above. Evaporation of the solvent followed by addition of EtOAc resulted in crystallization of a *photodimer* **18** (~ 20%) which after several crystallizations from benzene or EtOAc had m.p. 230–231·5° (Found: C, 67·17, H, 7·46; N, 8·03%; M$^+$ 358 (mass spec). $C_{20}H_{26}N_2O_4$ requires: C, 67·02; H, 7·31; N, 7·82%; M. W. 358); ν_{max} 1704 (conj. C═O); 1591 (C═C) cm^{-1}; λ_{max} 305 nm (ε 45,600).

The mother liquors from the above dimer were evaporated to dryness and chromatographed on alumina (Woelm, neutral, Act. I) eluting with benzene-(5-20%) ether. Repeated chromatography and crystallization from benzene-hexane afforded 3,5-*diacetyl*-1,2-*dihydro*-1-*methylpyridine* (**19**; 5·8 mg) as unstable orange crystals m.p. 155–157° (Found: C, 66·75; H, 7·32; M$^+$ 179 (mass spec). $C_{10}H_{13}NO_2$ requires: C, 67·02; H, 7·31%; M.W. 179); ν_{max} 1655 (conj. C═O), 1605 (C═C) cm^{-1}; λ_{max} 412, 316, 228 nm (ε 7600, 23,500, 11,900); NMR δ 2·20 (s, 3-COCH$_3$), 2·34 (s, 5-COCH$_3$), 3·08 (s, NCH$_3$), 4·29 (s, 2-H), 7·54 (m, 4-H), 7·59 (m, 6-H).

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