Photolysis of Methyl [6-^{2}H]2-Pyridylacetate. Selective Distribution of Deuterium Labelling

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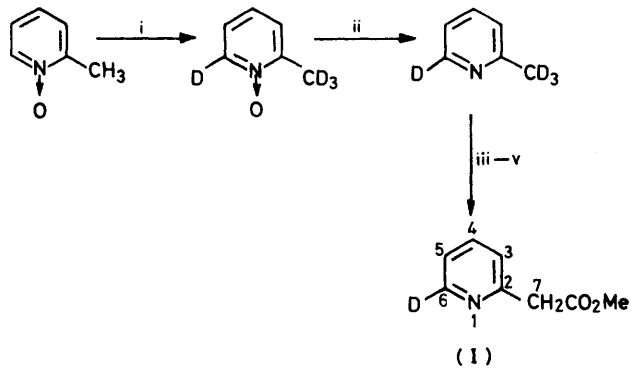
Photolysis of methyl [6-^{2}H]2-pyridylacetate (I) gave ring-deuteriated methyl anthranilate (II) in 20% yield together with recovered methyl 2-pyridylacetate (III) (6%). The isolated anthranilates were found by n.m.r. spectroscopy to contain approximately equal amounts of [4-^{2}H]- (IV) (40—45%) and [6-^{2}H]-isomers (V) (35—40%) with small amounts of the other two deuteriated positional isomers (20—10%). The recovered methyl 2-pyridylacetate (III) contains *ca.* 90% of the original deuterium at the 6-position. The labelling patterns are in accord with the formation of a diradical intermediate involving scission of the N(1)–C(6) bond of the pyridine ring and bond formation between C(4 or 6) and (7).

THE photochemical rearrangement of methyl 2-pyridylacetate to methyl anthranilate takes place with ring cleavage and recombination.[1] Analysis of the results from experiments with methyl 2-pyridylacetate labelled with a methyl group in the ring indicates exchange of the ring nitrogen with a side-chain carbon atom, but no exchange with the other carbon atoms.[2] However, the interpretation of mechanism is not conclusive, because irradiation of methyl 4-methyl-2-pyridylacetate affords a considerable amount of methyl-scrambled anthranilates, and also because methyl 6-methyl-2-pyridylacetate is photochemically inert in contrast to other isomers. Therefore, a methyl group may have electronic and steric effects which may affect the nature of the re-

[1] Y. Ogata and K. Takagi, *J. Amer. Chem. Soc.*, 1974, **96**, 5933.
[2] K. Takagi and Y. Ogata, *J.C.S. Perkin II*, 1977, 1148.

arrangement. Deuterium labelling would avoid this complication, and we chose methyl [6-^{2}H]2-pyridylacetate (I) as the substrate. The overall synthesis of (I) is shown in Scheme 1.*

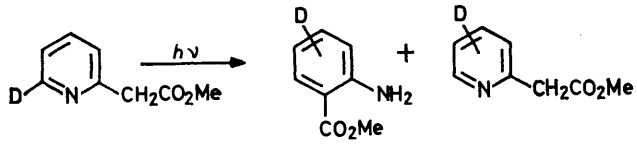
Irradiation of (I) was carried out for 11 h in dilute (7.7×10^{-3}M) diethyl ether–t-butyl alcohol (1 : 1 v/v).



(I)

SCHEME 1 Reagents: i, D_2O–NaOD in dioxan; ii, PCl_3 in $CHCl_3$; iii, PhLi; iv, CO_2; v, MeOH–HCl

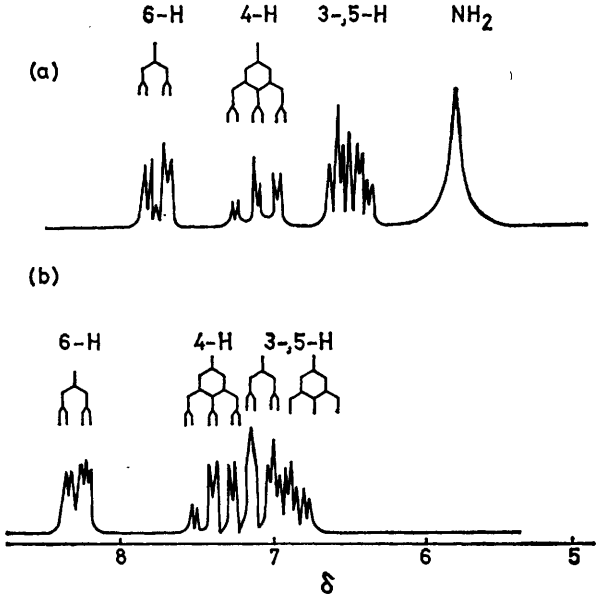
Preparative chromatography of the reaction mixture gave a deuteriated anthranilate (II) (20% isolated) and a deuteriated 2-pyridylacetate (III) (6% isolated).



(I) (II) (III)

Assignment of n.m.r. signals for ring protons at various positions of unlabelled anthranilate has been satisfactorily carried out by comparison with the corresponding protons in ring-methylated anthranilates,[2] and with the assistance of the decoupling technique [Figure (a)]. Thus, the proton at the 6-position of unlabelled methyl anthranilate appears as a complex doublet at low field (δ 7.65), and the 4-proton as a complex triplet at intermediate field (δ 7.10). The remaining two protons (3- and 5-positions) appear as a complex high field multiplet (δ 6.5). The three groups of signals are well separated.

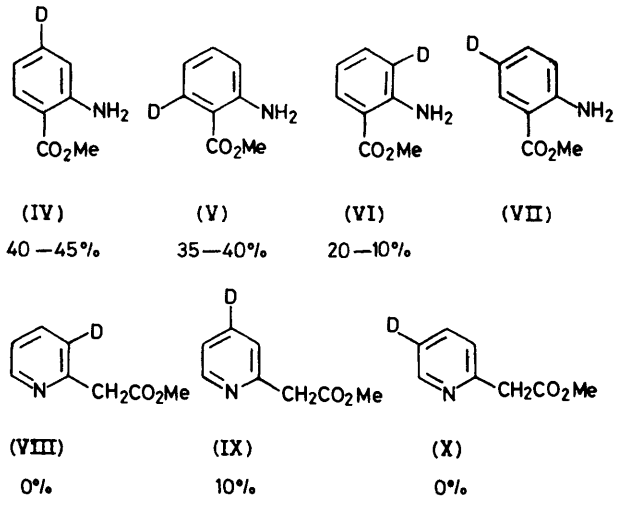
The n.m.r. spectrum of the photoproduct (II) may be analysed from these data. Within experimental error determined by the sensitivity of the n.m.r. technique (*ca.* 5%), 40—45% of product (IV), 35—40% of product (V), and 20—10% of a mixture of products (VI) and/or (VII) were obtained. Similarly, the recovered acetate (III) consisted of *ca.* 90% of product (I) and *ca.* 10% of the 4-deuterio-isomer (IX). Other deuterium-scrambled products [(VIII) and (X)], were not observed by n.m.r. analysis [Figure (b)]. It was established from the n.m.r. data that the total deuterium contents of the



Partial n.m.r. spectra of (a) methyl anthranilate and (b) methyl 2-pyridylacetate

starting material (I) and the products (II) and (III) were the same, and thus no deuterium is lost by photo-induced exchange reactions. It is difficult to eliminate the possibility of photoinduced hydrogen (deuterium) shifts, but such intramolecular processes are unlikely if the ring protons do not undergo intermolecular exchange reactions.

The formation of (IV) and (V) in similar yields can be explained by a mechanism *via* (XI) which has been



(IV) (V) (VI) (VII)

40—45% 35—40% 20—10%

(VIII) (IX) (X)

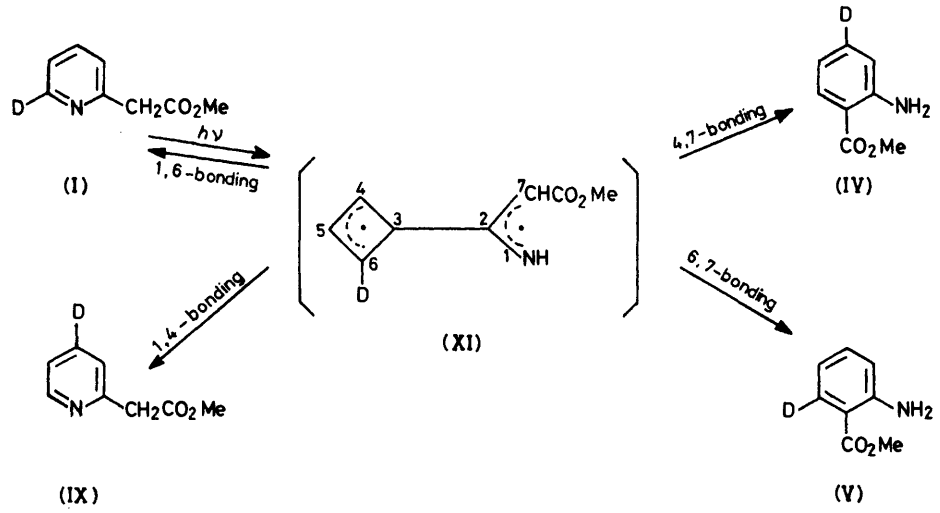
0% 10% 0%

SCHEME 2

proposed previously (Scheme 2).[2] Reversion to the acetate (I) or (IX) from (XI) may be more unfavourable than formation of anthranilates (IV) or (V) in view of the

* It is noted that virtually no deuterium was lost from the 6-position in the reactions leading to (I) although the deuterium atoms at position 7 were completely replaced.

fact that the expected statistical product ratio [(I)] : [(IX)] = 1 : 1 was not established for conversions of over 90%. This is presumably because of the difference in thermodynamical stability of the acetate and anthranilate structures. Indeed, product formation was predominant compared with reversion in the case of methyl 4-methyl-2-pyridylacetate.[2] Thus, the results support the intervention of (XI) during the rearrangement.



EXPERIMENTAL

G.l.c. analyses were carried out on a Hitachi gas chromatograph, type K 53, fitted with a 1.7 m PEG 20M column with a temperature range of 100—220° increasing at 10° min^{-1}. The n.m.r. spectra were obtained using a Hitachi R-24B spectrometer; samples were dissolved in CCl_4 with Me_4Si as internal standard.

Methyl [6-^{2}H]2-*Pyridylacetate* (I).—To sodium methoxide (0.68 g, 0.016 mol) in D_2O (6 ml; >99% D) and dioxan (20 ml) was added freshly distilled 2-picoline *N*-oxide (10.8 g, 0.1 mol). After refluxing for 4 h at 140—150° (bath temperature) deuteriated 2-picoline *N*-oxide (8.8 g) was obtained, b.p. 110° at 4 mmHg. N.m.r. spectral analysis indicated a deuterium content of *ca.* 58% both at the 6-position and the methyl protons, near to complete equilibrium for H–D exchange with D_2O (theoretical value 60%). The treatment was twice repeated to afford [α,6-$^2H_4$]2-picoline *N*-oxide, b.p. 110° at 4 mmHg (deuterium content 76.9% by n.m.r.), δ 8.25 (0.23 H, m), 7.2 (3 H, m), and 2.55 (0.69 H, s). The deuteriated *N*-oxide (20.2 g) was deoxygenated by refluxing with phosphorus trichloride (60 g) in chloroform (50 ml) to yield [α,6-$^2H_4$]2-picoline [3] (17 g), b.p. 129°, δ 8.45 (0.23 H, d, *J* 9 Hz), 7.5 (1 H, m), 7.1 (2 H, m), and 2.55 (0.69 H, m). Methyl [6-^{2}H]2-pyridylacetate (I) was prepared from the deuteriated 2-picoline (11 g) by known procedures [4] in an overall yield of 34% (6 g), b.p. 102—103° at 7 mmHg, δ(CCl_4) 8.34 (0.23 H, complex d, 6-H), 7.34 (1 H, dt, *J* 2 and 8 Hz, 4-H), 7.03 (2 H, m, H-3 and -5), 3.67 (2 H, s, CH_2), and 3.59 (3 H, s, OCH_3), M^+ 152.

Photolysis of Methyl [6-^{2}H]2-*Pyridylacetate* (I).—A solution (0.53 g, 7.7 × 10^{-3}M) of (I) in diethyl ether–t-butyl alcohol (150 ml; 1 : 1 v/v) was irradiated by a 300 W high pressure mercury lamp (Halos HIP 300). Blue fluorescence appeared after irradiation for 1 h. Irradiation was continued for 11 h, and the mixture was condensed *in vacuo* and chromatographed using a silica gel slurry in benzene. Fractions 10—60 (each fraction 5 g) contained (II) (105.4 mg, 20%), with a retention time identical with that of methyl anthranilate, δ(CCl_4) 7.65 (0.67 H, m, 6-H), 7.1 (0.67 H, complex t, 4-H), 6.5 (1.89 H, m, 3- and 5-H), 5.6br (2 H, s, NH_2), and 3.75 (3 H, s, OCH_3), M^+ 152. N.m.r. integration indicates that (II) has the isomeric distribution (IV) (43%), (V) (43%), and (VI) and/or (VII) (14%). In an independent experiment, n.m.r. analysis of (II) indicated the presence of (IV) (44%), (V) (35%), and (VI) and/or (VII) (21%).

Fractions 82—87 [eluant benzene–ethyl acetate (4 : 1)] yielded (III) (35 mg, 6%), with a retention time identical with that of methyl 2-pyridylacetate, δ(CCl_4) 8.34 (0.31 H, complex d, 6-H), 7.34 (0.92 H, dt, *J* 2 and 8 Hz, 4-H), 7.03 (2 H, m, 3- and 5-H), 3.67 (2 H, s, CH_2), and 3.59 (3 H, s, OCH_3). N.m.r. integration indicates that (III) consisted of *ca.* 90% (I) and *ca.* 10% (IX). The other positional isomers (VIII) and (X) were not formed.

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[3] (*a*) E. Ochiai, *J. Pharm. Soc. Japan*, 1951, **71**, 1385; (*b*) J. Vozza, *J. Org. Chem.*, 1962, **27**, 3856.

[4] R. B. Woodward and E. C. Kornfeld, *Org. Synth.*, 1955, Coll. Vol. 3, 413.