Photochemical Reactions of *N*-Phenylacetyl and *N*-(2-Iodophenylacetyl) Derivatives of 1,2,3,3a,4,5-Hexahydroindol-6-one [1]

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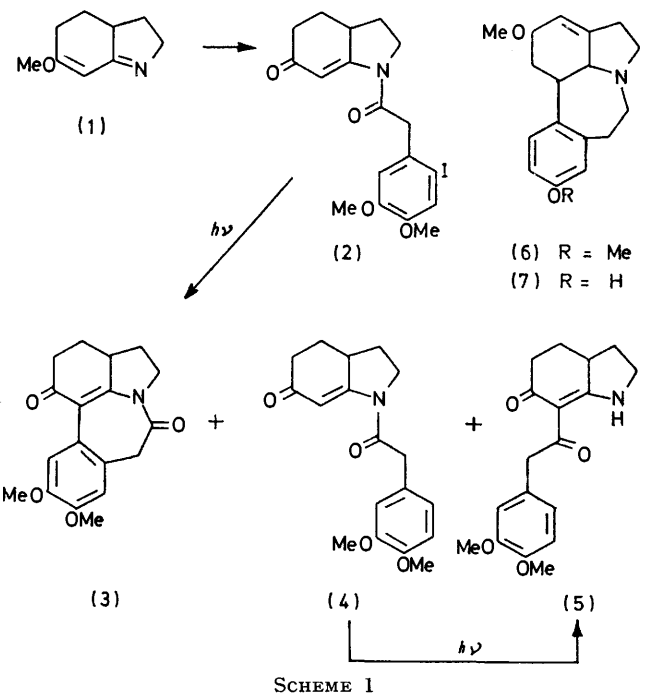
Irradiation of 1,2,3,3a,4,5-hexahydro-*N*-(2-iodo-4,5-dimethoxyphenylacetyl)indol-6-one (2) gave 3,3a,4,5-tetrahydro-10,11-dimethoxyindolo[7,1-*ab*][3]benzazepine-1,7(2*H*,8*H*)-dione (3) and the deiodination product (4). The latter (4) then underwent a photo-Fries rearrangement to 1,2,3,3a,4,5-hexahydro-7-(3,4-dimethoxyphenylacetyl)indol-6-one (5), which, upon further irradiation, gave 3,3',4,4'-tetramethoxybibenzyl (13), 2,3,3a,4,5,6-hexahydro-6-oxo-1*H*-indole-7-carbaldehyde (12), and -7-carboxylic acid (14). The production of compounds (12)—(14) is accounted for by a mechanism involving a type I cleavage and subsequent keten formation. The presence of a keten intermediate was demonstrated by nucleophilic addition of water, an alcohol, or an amine.

RECENTLY we have developed [2] a convenient general procedure for the preparation of enamido-ketones by the reactions of the imino-enol ether (1) † with acid chlorides. *N*-Benzoyl-1,2,3,3a,4,5-hexahydroindol-6-ones so produced were photocyclised to give the pyrrolo-[3,2,1-*de*]phenanthridine ring system,[2] presumably *via* a concerted electrocyclic process. We now report a study of the photochemical behaviour of the *N*-phenylacetyl analogues.

We envisaged that photocyclisation of an enamido-ketone of this type would give the indolobenzazepine ring system *via* a homolytic process. Intramolecular arylation *via* photolysis of a carbon–halogen bond providing nitrogen heterocycles has been well documented. However the majority of these reactions can be essentially regarded as involving formation of a biphenyl system,[3] and there has been no information related to the arylation of enamido-ketones. We also envisaged the photorearrangement of the enamido-ketone followed by an α-cleavage process to give products derived from the resulting radicals.

Treatment of the imino-enol ether (1) with 2-iodo-4,5-dimethoxyphenylacetyl chloride in the presence of aqueous potassium carbonate resulted in *N*-acylation with C–O bond cleavage *in situ* to give the enamido-ketone (2) (89%). Irradiation of (2) in the presence of triethylamine afforded the cyclisation product (3) (10%) together with the deiodination product (4) (23%) and the rearrangement product (5) (14%). The n.m.r. spectrum of the cyclisation product (3) showed no vinylic proton signal, and one of two aromatic proton singlets appeared at lower field (δ 7.16) than usual, indicating that the C-12 proton is in the deshielding zone of the 1-oxo-group. The 8-methylene proton signals appeared as an AB quartet; free rotation of the methylene group cannot occur in the cyclised structure. This cyclisation may provide synthetic access to cocculine (6) and cocculidine (7).[4]

The deiodination product (4) was identical with a sample obtained by an alternative synthesis (see later). The structure of the third product (5) was suggested by its mass spectrum, elemental analysis, and i.r. and n.m.r. spectra. The n.m.r. absorption pattern in the region



SCHEME 1

δ 1.5—4.0 (9 H) was closely similar to that of the deiodination product (4), indicating the presence of the 1,2,3,3a,-4,5-hexahydroindol-6-one system as a common structural unit, and there was no vinylic proton signal at δ *ca.* 6.7.

The formation of these products may be explained in terms of intramolecular arylation *via* photolysis, leading to the indolobenzazepine (3), which occurs competitively with hydrogen transfer to give the deiodination product

† The former conjugated diene structure [2a] for this compound, prepared by the Birch reduction of 6-methoxyindoline, was revised to the tautomeric form (1) on the basis of spectral and chemical evidence.[2b]

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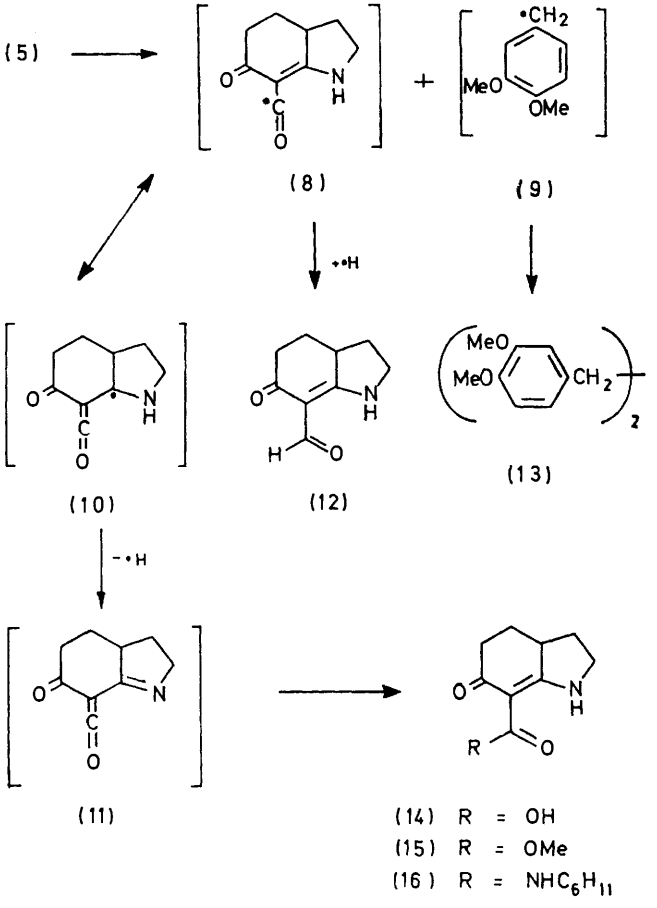
(4); the product (4) then undergoes a photo-Fries rearrangement to give (5).

When the deiodination product (4), prepared from the imino-enol ether (1) and 3,4-dimethoxyphenyl acetyl chloride, was itself irradiated, the rearrangement product (5) (27%), the bibenzyl (13) (18%), and the carboxylic acid (14) (5%) were obtained. A mechanism which accounts for the formation of compounds (13) and (14) is shown in Scheme 2, involving an initial Norrish type I cleavage which produces the acyl (8) and the benzyl (9) radicals, followed by loss of a hydrogen atom to give the keten (11) and dimerisation to give the bibenzyl (13), respectively. The carboxylic acid (14) may arise by nucleophilic addition of adventitious water to the keten



SCHEME 2

(11). The photochemical α-cleavage process in (5) parallels the mass spectral fragmentation [*m/e* 164 (100%)], which reflects the lability of the corresponding C–C bond.

Further evidence for the formation of a keten from the rearrangement product (5) was obtained from the following trapping experiments. Irradiation of (5) in the presence of a large excess of water gave the carboxylic acid (14) (33%) and the bibenzyl (13) (28%) along with the aldehyde (12) (15%). Irradiation of (5) in methanol gave the corresponding ester (15) (40%), the bibenzyl (13) (18%), and the aldehyde (12) (14%). The intermediate keten would be expected to be more efficiently trapped by a more powerful nucleophile. Accordingly (5) was irradiated in the presence of cyclohexylamine, to give the corresponding amide (16) in 82% yield and the bibenzyl (13) (35%), but no aldehyde was observed. We suggest that the formation of the aldehyde (12) [by hydrogen abstraction from the solvent by the acyl radical (8)] competes with keten formation.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro apparatus. U.v. spectra were measured with a Hitachi 124 spectrometer for ethanolic solutions; i.r. spectra with a Hitachi 215 grating spectrophotometer for solutions in chloroform; and mass spectra with a Hitachi RMU-7L double-focusing spectrometer at 70 eV. N.m.r. spectra were recorded at 100 MHz with a JEOL JNM-PS-100 spectrometer for solutions in deuteriochloroform containing tetramethylsilane as internal standard. Merck thin layer plates precoated with silica gel F_{254} (0.25 and 0.5 mm thick) were used for analytical and preparative t.l.c., respectively.

1,2,3,3a,4,5-Hexahydro-N-(*2-iodo-4,5-dimethoxyphenylacetyl*)*indol-6-one* (2).—To a solution of 2-iodo-4,5-dimethoxyphenylacetic acid (2.6 g) in dry chloroform (20 ml) was added thionyl chloride (1.0 g), and the mixture was kept at room temperature for 1 h. The excess of thionyl chloride was removed *in vacuo* to give the oily acid chloride. This material in dry chloroform (30 ml) was added simultaneously with aqueous 5% potassium carbonate (30 ml), during 30 min, to a stirred solution of the imino-enol ether (1) (1.2 g) in chloroform (50 ml) at 5—10 °C, and stirring was continued for an additional 30 min at 5—10 °C. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation left a pale yellow solid which was recrystallised from chloroform–hexane to give white *prisms* [3.0 g, 86% based on (1)], m.p. 213—214° (Found: C, 48.9; H, 4.5; N, 3.05. $C_{18}H_{20}INO_4$ requires C, 49.0; H, 4.55; N, 3.15%); $\lambda_{max.}$ 238 (log ε 4.08) and 286 nm (4.34); $\nu_{max.}$ 1 685 (ketone C=O), 1 640 (amide C=O), and 1 600 cm^{-1} (C=C); δ 3.79 (3 H, s, OMe), 3.81 (5 H, s, CH_2Ph and OMe), 6.61 (1 H, d, $J_{3a,7}$ 2 Hz, olefinic), 6.70 (1 H, s, 6′-H), and 7.15 (1 H, s, 3′-H); *m/e* 441 (5%, M^+), 314 (100, $M^+ - I$), and 304 (34, PhCH:C:O).

Irradiation of 1,2,3,3a,4,5-*Hexahydro*-N-(*2-iodo-4,5-dimethoxyphenylacetyl*)*indol-6-one* (2).—A solution of the enamido-ketone (2) (1.0 g) and triethylamine (2.0 g) in dry dioxan (450 ml) was flushed with nitrogen for 1 h and irradiated under nitrogen with a 6 W low-pressure mercury arc (Ushio) at room temperature. After 95 h, when t.l.c. [chloroform–acetone (10 : 1 v/v)], showed the disappearance of most of the starting material, the solvent was evaporated off *in vacuo*. The residue was chromatographed on silica gel (30 g). Elution with benzene gave a viscous oil (230 mg) which was purified by multiple preparative t.l.c. Two developments with benzene–methanol (10 : 1 v/v) separated two major components. The faster moving product was recrystallised from benzene–hexane to give *3,3a,4,5-tetrahydro-10,11-dimethoxyindole*[7,1-ab][3]*benzazepine*-1,7(2H, 8H)-*dione* (3) (69 mg, 10%) as white prisms, m.p. 196.5—197° (Found: C, 69.2; H, 6.2; N, 4.5. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.45%); $\lambda_{max.}$ 221 (log ε 4.43), 249 (4.25), 292 (4.00), and 315infl nm (3.87); $\nu_{max.}$ 1 685sh, 1 675sh, and 1 650 (C=O) and 1 605 cm^{-1} (C=C); δ 3.27 and 3.59 (2 H, AB-type q, *J* 13 Hz, 8-H_2), 3.90 (6 H, s, 2 × OMe),

6.75 (1 H, s, 9-H), and 7.16 (1 H, s, 12-H); *m/e* 313 (100%, M^+). The slower moving component was recrystallised from benzene–hexane to give 1,2,3,3a,4,5-*hexahydro*-7-(3,4-*dimethoxyphenylacetyl*)*indol*-6-*one* (5) (102 mg, 14%) as white needles, m.p. 92—93° (Found: C, 68.85; H, 6.85; N, 4.3. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.7; N, 4.45%); $\lambda_{max.}$ 225 (log ε 4.04), 262 (4.30), and 281 nm (4.35); $\nu_{max.}$ 3 250 (NH) and 1 600 cm^{-1} (C=O and C=C); δ 3.84 (6 H, s, 2 × OMe), 4.27 (2 H, s, CH_2Ph), 6.79 (3 H, s, ArH), and 10.4br (1 H, s, NH exchangeable with D_2O); *m/e* 315 (24%, M^+), 164 (100), and 151 (5).

Further elution of the silica gel column with benzene–ethyl acetate (20 : 1 v/v) gave 1,2,3,3a,4,5-*hexahydro*-N-(3,4-*dimethoxyphenylacetyl*)*indol*-6-*one* (4) (161 mg, 23%) as white scales, m.p. 143—144° (from benzene–hexane) (Found: C, 68.35; H, 6.7; N, 4.3. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.7; N, 4.45%); $\lambda_{max.}$ 229infl (log ε 3.90) and 286 nm (4.32); $\nu_{max.}$ 1 685 (ketone C=O), 1 640 (amide C=O), and 1 600 cm^{-1} C=C); δ 3.74 (2 H, s, CH_2PH), 3.86 (6 H, s, 2 × OMe), and 6.77 (4 H, m, olefinic and ArH); *m/e* 315 (100%, M^+) and 178 (100, PhCH:C:O).

1,2,3,3a,4,5-*Hexahydro*-N-(3,4-*dimethoxyphenylacetyl*)-*indol*-6-*one* (4) *from the Imino-enol Ether* (1).—To a solution of the imino-enol ether (1) (2.8 g) and triethylamine (2.1 g) in dry benzene (20 ml) a solution of 3,4-dimethoxyphenylacetyl chloride (4.0 g) in dry benzene was added dropwise over 30 min with stirring at 5—10 °C. After stirring for a further 30 min, the solution was washed with water then 5% hydrochloric acid and dried ($MgSO_4$). Removal of the solvent and recrystallisation of the residual solid from benzene–hexane gave the enamido-ketone (4) [3.3 g, 57% based on (1)], identical (t.l.c., mixed m.p., and i.r. and n.m.r. spectra) with the material isolated from the photolysis of (2).

Irradiation of 1,2,3,3a,4,5-*Hexahydro*-N-(3,4-*dimethoxyphenylacetyl*)*indol*-6-*one* (4).—A solution of the enamido-ketone (4) (1.08 g) in dioxan (350 ml) was purged with nitrogen for 1 h then irradiated as for the iodo-compound (2). Irradiation was discontinued after 110 h, at which time no starting material remained (t.l.c.). The solution was evaporated *in vacuo* to leave a dark viscous oil which was chromatographed on silica gel (50 g). Elution with benzene gave 3,3′,4,4′-tetramethoxybibenzyl (13) (136 mg, 18%) as white needles, m.p. 110.5—111° (from benzene–hexane) (lit.,[5] 109—110°), δ 6.85—6.57 (6 H, m, ArH), 3.83 (12 H, s, 4 × OMe), and 2.83 [4 H, s, $(PhCH_2)_2$]; *m/e* 302 (100%, M^+), 151 (97), and 106 (57). Elution with chloroform gave the rearrangement product (5) (491 mg, 27%) as white needles, m.p. 92—93° (from benzene–hexane), identical with the sample from the photolysis of (2). Further elution with chloroform–ethyl acetate (90 : 10 v/v) gave the unchanged enamido-ketone (4) (463 mg, 26%), then 2,3,3a,4,5,6-*hexahydro*-6-*oxo*-1H-*indole*-7-*carboxylic acid* (14) (48 mg, 4.6%), which crystallised from benzene–hexane as white needles, m.p. 177—179° (sublimed at *ca.* 165°) (Found: C, 59.85; H, 6.05; N, 7.65. $C_9H_{11}NO_3$ requires C, 59.65; H, 6.1; N, 7.75%); $\nu_{max.}$ 3 305 (NH), 1 675 (carboxy C=O), 1 610 (ketone C=O), and 1 570 cm^{-1} (C=C); δ 9.44br (1 H, s, NH exchangeable with D_2O) and 14.19br (1 H, s, OH exchangeable with D_2O); *m/e* 181 (56%, M^+) and 137 (100).

Irradiation of the Rearrangement Product (5).—(a) *In the presence of water.* A solution of the product (5) in acetonitrile (40 ml) and water (40 ml) was degassed for 20 min with nitrogen, then irradiated with a 100 W high-pressure mercury arc (Ushio) under nitrogen for 48 h. The solution was evaporated *in vacuo* to give a gum which was separated into three major components by multiple (× 2) preparative t.l.c. [chloroform–acetone (7 : 1 v/v)]. The fastest moving band, after elution and recrystallisation, gave the bibenzyl (13) (10 mg, 28%), identical with the material described above. The second component isolated was recrystallised from benzene–hexane to afford white prisms (6 mg, 15%), m.p. 143—144°, of 2,3,3a,4,5,6-*hexahydro*-6-*oxo*-1H-*indole*-7-*carbaldehyde* (12) (Found: C, 65.35; H, 6.6; N, 8.15. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.7; N, 8.5%); $\nu_{max.}$ 3 300 (NH), 1 650 (aldehyde C=O), 1 610 (ketone C=O), and 1 567 cm^{-1} (C=C); δ 9.70br (1 H, s, NH exchangeable with D_2O) and 9.80 (1 H, s, CHO); *m/e* 165 (30%, M^+), 137 (70), and 109 (100). The last band contained the carboxylic acid (14) (14 mg, 33%), identical with the material already obtained.

(b) *In methanol.* The product (5) (70 mg) in anhydrous methanol (70 ml) was irradiated as in (a). The solvent was removed and the residue was separated into three products by preparative t.l.c. [as in (a)]. The fastest running band gave the bibenzyl (13) (6 mg, 18%) and the second band the aldehyde (12) (5 mg, 14%). Each product was identical with the specimen already obtained. The last band, after elution and recrystallisation, yielded *methyl* 2,3,3a,4,5,6-*hexahydro*-6-*oxo*-1H-*indole*-7-*carboxylate* (15) (17 mg, 40%) as white needles, m.p. 94—95° (from benzene–hexane) (Found: M^+, 195.088 9. $C_9H_{13}NO$ requires M, 195.089 5); $\nu_{max.}$ 3 340 (NH), 1 660 (ester C=O), 1 633 (ketone C=O), and 1 580 cm^{-1} (C=C); δ 3.75 (3 H, s, OMe), and 9.20br (1 H, s, NH exchangeable with D_2O); *m/e* 195 (40%, M^+) and 167 (100).

(c) *In the presence of cyclohexylamine.* The product (5) (106 mg) and cyclohexylamine (340 mg) in dry benzene (80 ml) were irradiated as in (a). Removal of the solvent and unchanged cyclohexylamine by distillation under reduced pressure, followed by preparative t.l.c. as in (a), gave as the less polar fraction the bibenzyl (13) (19 mg, 37%). The more polar fraction yielded N-*cyclohexyl*-2,3,3a,4,5,6-*hexahydro*-6-*oxo*-1H-*indole*-7-*carboxylic acid* (16) (72 mg, 82%) as white needles, m.p. 165—166° (from chloroform–hexane) (Found: C, 68.55; H, 8.35; N, 10.7. $C_{15}H_{22}N_2O_2$ requires C, 68.65; H, 8.45; N, 10.7%); $\nu_{max.}$ 3 250 (NH), 1 615 (ketone and amide C=O), and 1 540 cm^{-1} (C=C); δ 9.65br and 10.22br (each 1 H, s, NH exchangeable with D_2O); *m/e* 265 (36%, M^+) and 164 (100).

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