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PHOTO-OXIDATION OF INDAZOLES

THE FORMATION OF BENZOXAZEPOINDAZOLES

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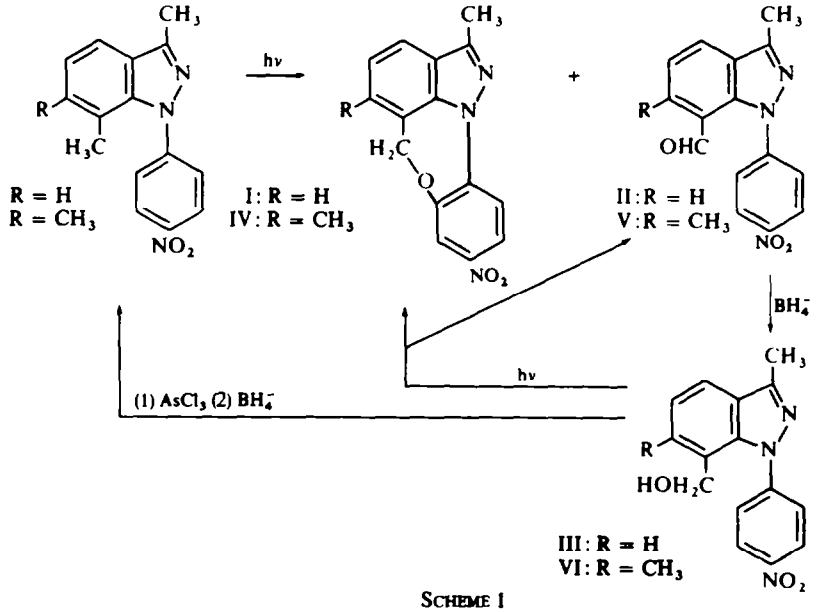
Abstract—The UV irradiation of 1-(*p*-nitrophenyl)-3,7-dimethylindazoles leads to the formation of the corresponding 7-formyl derivatives together with 2-methyl-9-nitro-6 *H*-[1.5]benzoxazepo[3.5-*h*, *i*]indazoles.

THE UV irradiation of Me derivatives of the 1-(*p*-nitrophenyl) indazole afforded formylindazoles as products of the photoconversion $R—CH_3 \rightarrow R—CHO$.[1-3]

This reaction was observed when the Me group was located at positions 3, 4 or 5 of the indazole ring, but no oxidation occurs of an alkyl group joined to the position 6.

The photochemical reactions of 7-Me substituted 1-(*p*-nitrophenyl)-3-methylindazoles yield the expected aldehydes together with benzoxazepoindazoles as result of a novel photo-cyclization between the substituents at positions 1 and 7.

The 1-(*p*-nitrophenyl)-3,7-dimethylindazole and the 1-(*p*-nitrophenyl)-3,6,7-trimethylindazole were irradiated in non-degassed acetic acid solutions with a high



SCHEME 1

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pressure Hg lamp (400 watts) as previously reported.[3] The photoproducts obtained, and their further transformations, are represented in the Scheme 1.

In the first case, the photomixture was resolved into two substances (I and II) by chromatographic procedures, whereas from the other indazole, the corresponding products (IV and V) together with the hydroxymethyl derivative VI was also obtained.

The structure of a benzoxazepoindazole was assigned to the first eluted compounds (I and IV) for the following reasons: The molecular formula showed, in each case, that these compounds have one O atom more than the original indazoles. Nevertheless, according to the IR spectra, this oxygen, incorporated during the photochemical reaction, is present neither as a CO function nor as an OH group. The maximal absorption of the UV spectra of each compound, is shifted to longer wavelengths with respect to that of the starting substance. The NMR spectra indicate that, in both examples, the 7-Me group has been transformed into a methylene group, and that one aromatic proton has been lost during the reaction. Besides, the NMR spectra does not show the typical signals of the *p*-nitrophenyl moiety.

In agreement with this, the UV irradiation of the hydroxymethyl derivatives III and VI afforded the cyclization products (I and IV) together with the aldehydes II and V respectively.

The position of the formyl group in the compounds II and V was established by correlation of the NMR data of these compounds, their hydroxymethyl derivatives and the starting indazoles, with the data previously reported.[3]

The indazole structure of the aldehydes II and V was demonstrated through the reaction sequence indicated in the Scheme 1.

DISCUSSION

We have postulated[3] that the primary photochemical process in this reaction, is the formation of a radical by abstraction of an H atom from the alkyl group:

$$R—CH_3 \xrightarrow{h\nu} R—CH_2\cdot + H\cdot$$

and that, the radical $R—CH_2\cdot$ can react with oxygen giving the hydroperoxide radical $R—CH_2OO\cdot$, which in the propagation step can give an hydroperoxide as follows:

$$R—CH_2OO\cdot + R—CH_3 \rightarrow R—CH_2OOH + R—CH_2\cdot$$

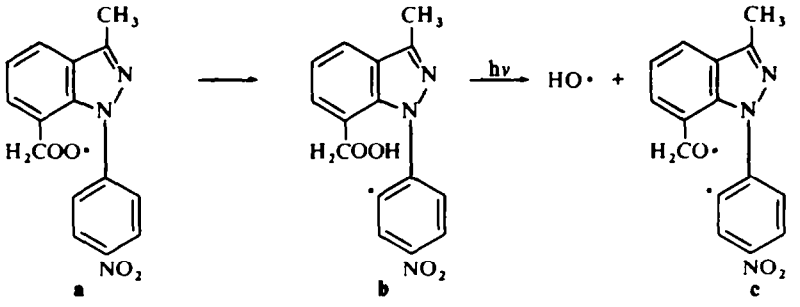
The hydroperoxide on photochemical transformation can give a radical $R—CH_2O\cdot$

$$R—CH_2OOH \xrightarrow{h\nu} R—CH_2O\cdot + HO\cdot$$

and this radical is probably an intermediate in the formation of aldehydes and hydroxymethyl compounds.

In the examples reported in this paper, the hydroperoxide radical may have the structure **a** (see Scheme 2) and this radical can abstract an H atom from the Me group of another molecule to give the corresponding hydroperoxide, which in turn, may be transformed, as previously indicated, in aldehydes and hydroxymethyl compounds.

To explain the formation of the cyclization products, we may consider that the H-donor is the *p*-nitrophenyl group of the same molecule, giving the radical **b**.



SCHEME 2

This radical through a photochemical process, can form the biradical **c**, which will cyclize to the benzoxazepoindazole.

The benzoxazepoindazoles and aldehydes obtained by UV irradiation of the 7-hydroxymethyl derivatives (see Scheme 1) may be interpreted, considering that in these cases, the primary photochemical process is the formation of the radical R—CH_2·, according to

$$R—CH_2OH \xrightarrow{h\nu} R—CH_2\cdot + HO\cdot$$

and this radical will react with oxygen to give **a**, which then follows the reaction sequence already described.

EXPERIMENTAL

M.ps are uncorrected. The UV spectra were determined on a Beckman DK-2A spectrophotometer. The NMR spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard. δ values are given. TFA, trifluoracetic acid.

Indazoles used in this work. The 1-(*p*-nitrophenyl)-3-methylindazoles used for the photochemical reactions, were prepared as described.[4]

1-(*p-Nitrophenyl*)-3,7-*dimethylindazole.* UV ($CHCl_3$) λ_{max} 356 nm (log ε 4·01); sh 292 (3·64); sh 258 (4·04). NMR ($AsCl_3$) 7-CH_3 2·12; 3-CH_3 2·97; $H_{4,5,6}$ 7·33–8·00; $H_{2',6'}$ 7·78; $H_{3',5'}$ 8·45.

1-(p-*Nitrophenyl*)-3,6,7-*trimethylindazole.* UV ($CHCl_3$) λ_{max} 363 nm (log ε 4·00); sh 262 (4·03). NMR ($AsCl_3$) 7-CH_3 1·98; 6-CH_3 2·48; 3-CH_3 2·93; H_5 7·41; H_4 7·75; $H_{2',6'}$ 7·75; $H_{3',5'}$ 8·42.

Irradiation of the 1-(p-*nitrophenyl*)-3,7-*dimethylindazole*

Formation of I *and* II. The compound mentioned (475 mg) was dissolved in AcOH (200 ml) and the soln was irradiated for 8 hr in the form already reported.[3]

The photomixture was worked up as in the previous examples and the products were isolated by chromatography on a silica-gel column, using a mixture of EtOAc-ligroin as eluent (2:100 for the elution of the first product and the non-converted starting material).

2-*Methyl*-9-*nitro*-6 H-[1.5] *benzoxazepo* [3.5-h, i] *indazole* (I). This was obtained by evaporation of the first eluted fraction (7 mg, yield 1·5%), yellow needles from EtOH, m.p. 233–235°. (Found: C, 63·92; H, 3·94; N, 14·54; O, 16·82. $C_{15}H_{11}N_3O_3$ requires: C, 64·04; H, 3·94; N, 14·94; O, 17·07%); UV ($CHCl_3$) λ_{max} 372 nm (log ε 4·25); sh 272 (3·73); NMR (TFA) 2-CH_3 3·13; CH_2 5·60; arom. prot. (6 H) 7·80–8·70.

From the second eluted fraction the non-converted starting indazole (350 mg) was obtained.

1-(*p-Nitrophenyl*)-3-*methyl*-7-*formylindazole* (II). The third fraction was eluted with EtOAc-ligroin (10:100) giving, by evaporation, a residue (71 mg, yield 15%) which was recrystallized from EtOH as yellow needles, m.p. 201–204°. (Found: C, 64·30; H, 4·15; N, 14·83. $C_{15}H_{11}N_3O_3$ requires: C, 64·04; H, 3·94; N, 14·94%); UV ($CHCl_3$) λ_{max} 339 nm (log ε 4·30); sh 290 (4·06); sh 240 (4·31). NMR ($AsCl_3$) 3-CH_3 2·92; $H_{4,5,6}$ 7·83–8·46; $H_{2',6'}$ 7·65; $H_{3',5'}$ 8·37; CHO 9·85.

Formation of the 1-(*p-nitrophenyl*)-3-*methyl*-7-*hydroxymethylindazole* (III) *by reduction of* II. The aldehyde II (90 mg), dissolved in a mixture of dioxan (50 ml) and water (2 ml), was reduced with $NaBH_4$ as previously

indicated.[3] The product obtained (89 mg) was recrystallized from benzene–ligroin as yellow needles, m.p. 152–153°. (Found: C, 63·48; H, 4·74; N, 14·72. $C_{15}H_{13}N_3O_3$ requires: C, 63·59; H, 4·63; N, 14·83%); UV ($CHCl_3$) λ_{max} 353 nm (log ε 3·98); sh 301 (3·54); sh 258 (3·99); NMR ($AsCl_3$) 3-CH_3 3·03; CH_2 4·97; $H_{4,5,6}$ 7·66–8·16; $H_{2',6'}$ 7·98; $H_{3',5'}$ 8·60.

Irradiation of the 1-(p-*nitrophenyl*)-3-*methyl*-7-*hydroxymethylindazole* (III)

Formation of I *and* II. The derivative III (32 mg), dissolved in $CHCl_3$ (15 ml), was irradiated for 45 min. The soln was concentrated and chromatographed through a silica-gel column employing $CHCl_3$ as eluent. By evaporation of the first fraction, a product (6 mg) was obtained, which was identified, after recrystallization from EtOH, as compound I by m.p. and IR.

The product obtained from the second fraction (10 mg) was recrystallized from EtOH, giving m.p. 201–204° and a IR spectrum identical to that of II.

Formation of the 1-(p-*nitrophenyl*)-3,7-*dimethylindazole from* III. The derivative III (20 mg) was treated with $AsCl_3$ (2 ml) and the soln was heated at 70° for 6 hr. After dilution with water, the product was extracted with $CHCl_3$. Evaporation of the solvent gave a residue that was dissolved in a mixture of dioxan–water (50:2) and to the soln was added an excess of $NaBH_4$. The mixture was heated at 70° for 2 hr and then extracted with $CHCl_3$. The evaporation residue was chromatographed on a silica-gel column using as eluent EtOAc–ligroin (3:100). From the first fraction the 1-(*p*-nitrophenyl)-3,7-dimethylindazole (6 mg) was obtained.

Irradiation of the 1-(p-*nitrophenyl*)-3,6,7-*trimethylindazole*

Formation of IV, V *and* VI. The irradiation was as in other cases.[3] The product was chromatographed on a silica-gel column using EtOAc–ligroin as eluent (2:100 for the elution of IV and the non-converted starting material).

2,5-*Dimethyl*-9-*nitro*-6 H-[1.5] *benzoxazepo* [3.5-h, i] *indazole* (IV). This obtained from the first eluted fraction, yellow needles from $CHCl_3$–EtOH (yield 7%), m.p. 261–262°. (Found: C, 64·90; H, 4·57; N, 14·38. $C_{16}H_{13}N_3O_3$ requires: C, 65·08; H, 4·44; N, 14·23%); UV ($CHCl_3$) λ_{max} 373 nm (log ε 4·32); sh 275 (3·93); NMR (TFA) 5-CH_3 2·66; 2-CH_3 3·10; CH_2 5·65; arom. prot. (5 H) 7·58–8·66.

From the second eluted fraction the original starting indazole (56%) was obtained.

1-(p-*Nitrophenyl*)-3,6-*dimethyl*-7-*formylindazole* (V). The product obtained from the third fraction (eluted with EtOAc–ligroin 20:100) resulted to be a mixture, and was re-chromatographed on a silica-gel column using $CHCl_3$ as eluent. The aldehyde V was obtained from the first fraction (yield 16%) and was recrystallized from EtOH giving yellow needles, m.p. 213–214°. (Found: C, 65·17; H, 4·29; N, 14·15. $C_{16}H_{13}N_3O_3$ requires: C, 65·08; H, 4·44; N, 14·23%); UV ($CHCl_3$) λ_{max} 340 nm (log ε 4·21); 300 (4·10); NMR ($AsCl_3$) 3-CH_3 3·00; 6-CH_3 2·97; H_5 7·65; H_4 8·30; $H_{2',6'}$ 7·75; $H_{3',5'}$ 8·53; CHO 9·68.

1-(p-*Nitrophenyl*)-3,6-*dimethyl*-7-*hydroxymethylindazole* (VI). This product (yield 20%) was eluted from the column mentioned above and purified through a silica-gel column using CH_2Cl_2 as elution solvent; yellow needles from benzene, m.p. 230–231°. (Found: C, 64·48; H, 5·12; N, 14·21. $C_{16}H_{15}N_3O_3$ requires: C, 64·63; H, 5·09; N, 14·14%); UV ($CHCl_3$) λ_{max} 355 nm (log ε 4·34); sh 300 (4·12); sh 265 (4·38); NMR ($AsCl_3$) 6-CH_3 2·65; 3-CH_3 2·96; CH_2 4·95; H_5 7·58; H_4 8·06; $H_{2',6'}$ 7·96; $H_{3',5'}$ 8·60.

Compound VI was also obtained by reduction of the aldehyde V with $NaBH_4$.

Irradiation of the 1-(p-*nitrophenyl*)-3,6-*dimethyl*-7-*hydroxymethylindazole* (VI)

Formation of IV *and* V. The derivative VI (53 mg), dissolved in AcOH (12 ml), was irradiated for 2 hr. The product was chromatographed on a silica-gel column using CH_2Cl_2 as eluent. From the first fraction, IV was obtained (8 mg) and identified by m.p. and IR. The aldehyde V (32 mg) was obtained from the second eluted fraction.

Formation of the 1-(p-*nitrophenyl*)-3,6,7-*trimethylindazole from* VI. The derivative VI (32 mg) was reduced by a similar method to that described for the reduction of III. The 1-(*p*-nitrophenyl)-3,6,7-trimethylindazole obtained (11 mg) was identified by m.p. and IR.

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