Pergamon

Tetrahedron Letters, Vol. 38, No. 4, pp. 621-622, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02379-9

Photolysis of Indomethacin in Methanol

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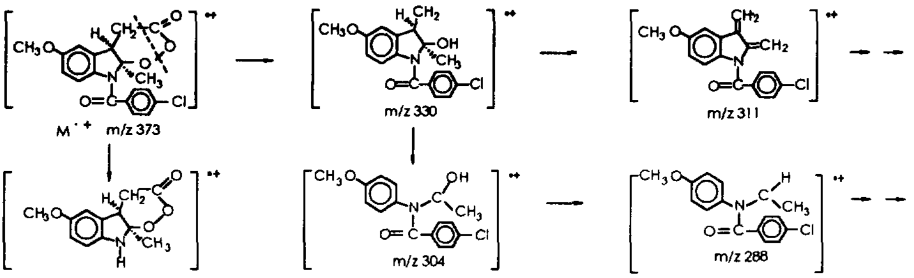
Abstract: A novel photo-oxidation product containing a six-membered 1,2-dioxane ring was isolated from the photolysis of indomethacin in methanol and a possible mechanism is proposed. © 1997, Published by Elsevier Science Ltd. All rights reserved.

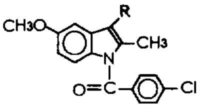
Indomethacin (IN) is used as an anti-inflammatory, antipyretic and analgesic therapeutic agent, however, it is photochemically labile. Weedon and Wong found that irradiation of IN in benzene using a medium pressure mercury lamp yielded **1** by decarboxylation of the acetic acid side chain; in methanol yielded **2** by further oxidation[1]. Similar results were observed by Dabestani, et al.[2]

We now report that when IN in methanol (27.9 m mol) was irradiated by daylight for 7 d, two major photolytic products, **5** and **6** were isolated by preparative HPLC[3] and their structures characterized[4,5]. The EI-MS of **6** revealed some interesting characteristics (Scheme 1). ^1H NMR of **6** shows the signal of methine hydrogen attached to C-3 at 2.54 ppm and methyl attached to C-2 at 1.74 ppm which are in accord with a *syn* relationship[6]. ^{13}C NMR of **6**, C-2 appears at 83.4 ppm and C-3 at 41.3 ppm which strongly imply both carbons becoming saturated. Attribution of protons of 1,2-dioxan-3-one ring system is achieved through examination of HETCOR and DEPT ^1H-^{13}C connectivities. These results clearly indicate that **6** contains an indoline ring[7].

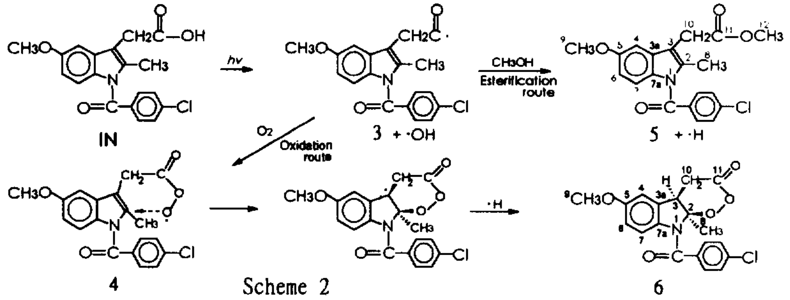


Scheme 1

Irradiation of IN in N_2-gassed or air-saturated benzene, several radical species were detected[2]. Thus the photolysis of IN in organic solvents via radical pathways were assumed. In our study, the formation of **5** and **6** was apparently not gone through the decarboxylation process; instead, we postulate that they were formed by acyl cleavage of the carboxylic group by sharing with a common intermediate, an acyl radical, **3** (Scheme 2). Starting from **3**, **5** was produced via an esterification route; **6** via an oxidation route by reacting with a molecular oxygen. The formation of **6**, 9-(4-chlorobenzoyl)-6-methoxy-9a-methyl-4,4a-dihydro-1,2-dioxa-9-aza-fluoren-3-one, represents one of an unprecedented example of intramolecular peracetate radical **4** addition to the 2 position of the indole ring leading to a six-membered 1,2-dioxane derivative.



	R
1	CH3
2	CHO



Scheme 2

Acknowledgments: The authors thank Cheng's Foundation for Pharmaceutical Sciences (CFPS-83004) and Taipei Medical Colege (83-D109) for financial support.

Reference and notes:

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2. Dabestani, R.; Sik, R. H.; Davis, D. G.; Dubay, G.; Chignell, C. F.*Photochem. Photobiol.*, **1993**, *58*, 367.
3. HPLC: Hitachi L-6200 pump, L-4200 detector at 254nm, Nucleosil 7 C_{18} column (250*4.6mm i.d.), mobile phase, CH_3OH:H_2O (1% acetic acid) = 75:25, flow rate: 2ml/min. Retention time: **6**, 7.50 min; **5**, 15.94 min. Yield of **6**=11.2 %; **5**=20.9 % (by integration) approaching maximum after 30 d of irradiation.
4. Methyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindolyl-3-acetate, **5**:Pale yellow needles, mp=85-87 ℃. ^1H NMR δ(ppm) $CDCl_3$ (500Hz): 6.94 (d, ^1H, J=8.7Hz, H-4), 6.62-6.65 (dd, 1H, J=8.8Hz, 2.6Hz, H-6), 6.83-6.86 (d, 1H, J=8.9Hz, H-7), 2.35(s, 3H, H-8), 3.80 (s, 3H, H- 9), 3.64 (s, 2H, H-10), 3.68 (s, 3H, H - 12). ^{13}C NMR δ(ppm) $CDCl_3$(500MHz): 130.53(C-2), 112.39 (C-3), 130.69 (C-3a), 101.22 (C-4), 155.95 (C-5), 111.48 (C-6), 114.83 (C-7), 139.08 (C- 7a), 13.19 (C-8), 55.57 (C-9), 29.98 (C-10), 171.18 (C-11), 52.00 (C-12). IR (KBr): 1736cm^{-1} (s,C=O). MS (70ev, m/z (%)): 371 (M+, 75), 327 (6), 312 (17), 139 (100).
5. 9-(4-Chlorobenzoyl)-6-methoxy-9a-methyl-4,4a,-dihydro-1,2-dioxa-9-aza-fluoren-3-one, **6**: Yellow crystals mp=217-218 ℃. ^1H NMR δ(ppm) CD_3COCD_3 (500MHz): 7.17 (d, 1H, H-4),6.78(dd, 1H, J=8.8,2.6 Hz, H-6), 6.84 (d, 1H, J=8.7 Hz, H-7), 2.54 (d, 1H, H-3), 1.74 (s, 3H, H-8), 3.79 (s, 3H, H-9), 3.19(d, 2H, J=6.1 Hz, H-10). ^{13}C NMR δ(ppm) CD_3COCD_3(500 MHz): 83.44 (C-2), 41.28 (C-3), 136.21 (C-3a), 110.55 (C-4), 158.05 (C-5), 117.01 (C-6),118.51 (C-7), 137.86 (C- 7a), 19.16 (C-8), 56.05 (C-9), 40.48 (C-10), 171.65 (C-11). IR (KBr): 1796 cm^{-1} (s, C=O). MS(70 ev, m/z (%)): 373 (M+, 100), 330 (13), 311(2), 288 (2), 234 (31), 217 (5), 190 (22), 175 (3), 139 (37).
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(*Received in China* 10 *August* 1996; *revised* 30 *August* 1996; *accepted* 18 *October* 1996)