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Photolytic Decomposition of *N*-(2,6-Dichloro-*m*-tolyl)anthranilic Acid (Meclofenamic Acid)

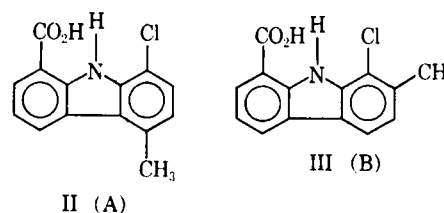
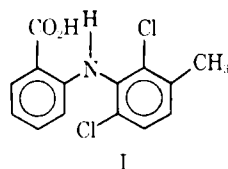
JOSE PHILIP[▲] and DALE H. SZULCZEWSKI

Abstract □ Exposure of dilute solutions of *N*-(2,6-dichloro-*m*-tolyl)anthranilic acid to visible or UV light results in fairly rapid decomposition with concurrent formation of approximately equimolar amounts of 8-chloro-7-methylcarbazole-1-carboxylic and 8-chloro-5-methylcarbazole-1-carboxylic acids.

Keyphrases □ *N*-(2,6-Dichloro-*m*-tolyl)anthranilic acid (meclofenamic acid)—isolation, identification of photolytic decomposition products □ Meclofenamic acid [*N*-(2,6-dichloro-*m*-tolyl)anthranilic acid]—isolation, identification of photolytic decomposition products □ Photolysis, *N*-(2,6-dichloro-*m*-tolyl)anthranilic acid (meclofenamic acid)—isolation, identification of decomposition products

N-(2,6-Dichloro-*m*-tolyl)anthranilic acid (meclofenamic acid)¹, I, is an investigational new drug being evaluated for use as an anti-inflammatory agent. Results from previous studies in these laboratories indicated that one possible route of decomposition involved decarboxylation to the corresponding substituted diphenylamine in accord with the general chemistry of anthranilic acids. This reaction, however, proceeds at an appreciable rate only at elevated temperatures (100° for strongly acidic solutions or above the melting point, 258.5–259.5° in the case of the solid state) and would have little relevancy to dosage form shelflife at near ambient temperatures.

As part of continuing preformulation studies, the



influence of light, as another condition of stress, was studied.

DISCUSSION

Sequential UV spectra obtained during exposure of a dilute solution of I (c 0.00426%, methanol) to visible light² are shown in Fig. 1. There was a fairly rapid spectral change during the initial period of exposure, after which the spectra become essentially constant. Spectra obtained from aqueous alkaline solutions exposed in the same manner were qualitatively similar, whereas like solutions stored in the dark gave spectra invariant with time.

A thin-layer chromatogram obtained on a methanolic solution of I (R_f 0.7) exposed to the point of spectral redundancy showed the formation of at least two reaction products (1, R_f 0.4; and 2, R_f 0.31), one of which predominated. Available data indicate that I undergoes a facile reaction in the presence of light, but the nature of this reaction is unknown. Relevant information from the literature is rather scarce; however, the work of Bowen and Eland (1) indicated that diphenylamine is converted to carbazole in the presence of light.

To determine the nature of this reaction, reaction products were isolated for identification. A large volume of a more concentrated methanolic solution of I was exposed to UV light³ (c 0.1%), and the solvent was removed under vacuum. The residue was recrystallized to remove residual I and the minor decomposition product. During the recrystallization, fractions were obtained whose R_f values were the same as the major decomposition product but whose

¹ Parke, Davis & Co.

² Light cabinet (a steel cabinet equipped with several 100-w. incandescent bulbs).

³ Hanovia Lethery germicidal lamps.

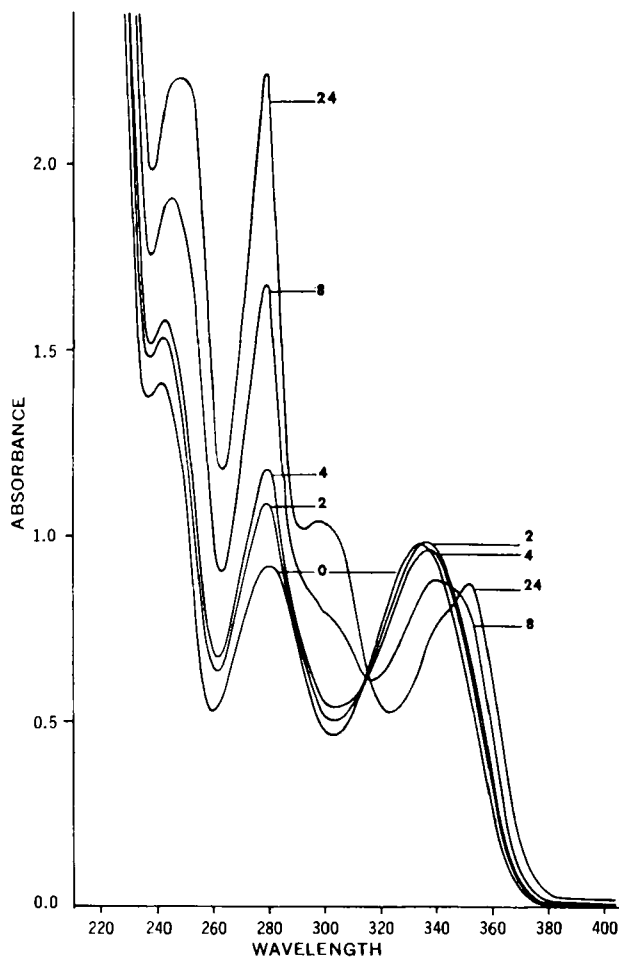


Figure 1—Sequential UV spectra of the photolysis of I in methanol. Exposure time (hours) is noted.

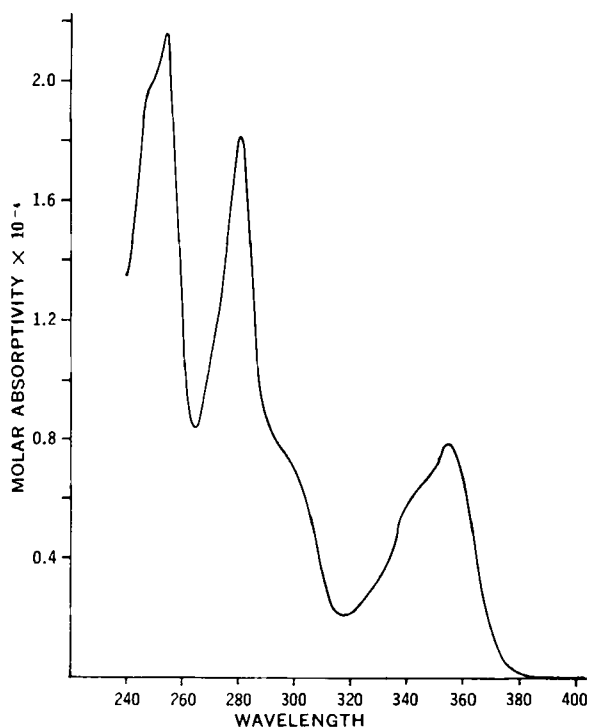


Figure 2—UV spectrum of II in 95% methanol-0.01 N hydrochloric acid.

Table I—IR Spectral Data for Fractions A and B (KBr Dispersion)

Group	Wave Number, cm^{-1}	
	A	B
—NH	3450 (sharp)	3460 (sharp)
—CO ₂ H	3300-2400 (broad)	3300-2400 (broad)
	1665 (strong)	1680 (strong)
CO ₂ H dimer	928	920

UV spectra differed. In particular, absorption near 300 nm. varied, taking the form of a shoulder in some and a distinct maximum in others (Figs. 2 and 3). The crystalline materials (A and B) giving these two spectra were investigated to determine structure.

The empirical formula, $\text{C}_{11}\text{H}_{10}\text{ClNO}_2$, as determined by elemental analysis and the molecular weight, 259, determined by mass spectroscopy for both A and B indicated that they were isomeric compounds, each differing from I by the elements of HCl. The presence of amino and carboxylic acid moieties in both was established from corresponding IR spectra (Table I). NMR spectra (Figs. 4 and 5 and Table II) were definitive and, together with preceding data and information, established the dominant photolytic products to be 8-chloro-5-methylcarbazole-1-carboxylic acid (II) and 8-chloro-7-methylcarbazole-1-carboxylic acid (III).

The relative amounts of II and III formed during photolysis were determined from the terminal UV spectrum of the spent reaction mixture. The observed absorbance ratio ($R_{\text{obs}} = A_{\lambda_{302}}/A_{\lambda_{351}}$) was 1.18, which indicated that the product distribution was 1:1.

EXPERIMENTAL⁴

Initial Photolysis Studies—Solutions of I, approximately 0.004%, were prepared in methanol and pH 9.0 phosphate buffer. Volumetric flasks containing 100-ml. aliquots of these solutions were placed in the light cabinet and sampled periodically for UV determination.

Preparation and Isolation of Major Photolysis Products—Two liters of a 0.1% methanolic solution of I was placed in a flat tray

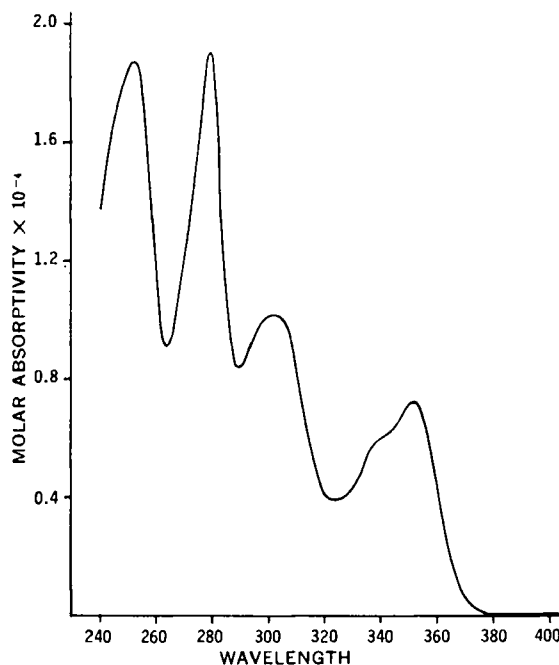


Figure 3—UV spectrum of III in 95% methanol-0.01 N hydrochloric acid.

⁴ UV spectra were determined using a Cary 14 spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrophotometer. IR spectra were taken in potassium bromide disks using a Perkin-Elmer 457 grating IR spectrophotometer. Thin-layer chromatograms were run using silica gel plates (Quantum Industries, QIF, 250 μ).

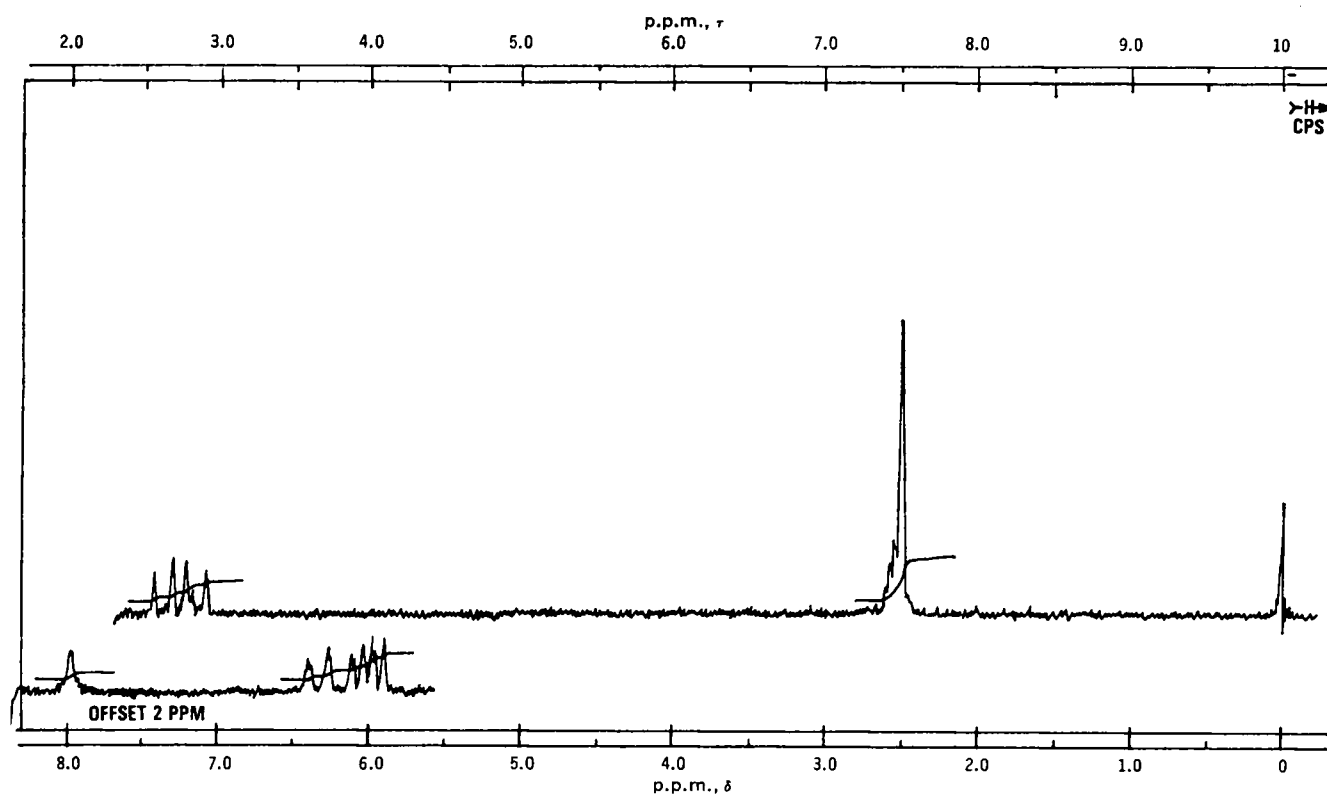
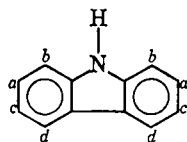


Figure 4—NMR spectrum of III in dimethyl sulfoxide- d_6 . For carbazole (acetone as solvent):



the following assignments are made (2) (p.p.m.): a, 7.17; b, about 7.45; c, 7.49; and d, 8.12.

and irradiated with three germicidal lamps³ resting on the rims of the tray. After the reaction was essentially complete (monitored by TLC and UV spectroscopy), the solvent was removed and the residue was recrystallized from ethyl acetate–isooctane to free it of residual I and other minor products (TLC).

A second recrystallization from ethyl acetate yielded a crystalline precipitate (A) whose UV spectrum (Fig. 2) differed from the terminal spectrum (Fig. 1) obtained during the reaction in that there was no maximum in the 302-nm. region. Material obtained from the mother liquor of this recrystallization (B) showed a distinct maximum in this region. Furthermore, A showed an absorption in its NMR spectrum at 2.70 p.p.m., whereas B showed two peaks in this region (2.70 and 2.50 p.p.m.). Fraction B was then repeatedly recrystallized until the compound contained in A was removed to yield crystalline material whose NMR spectrum showed only a single peak at 2.50 p.p.m. Both compounds had identical behavior

with regard to TLC [silica, chloroform–ethyl acetate–acetic acid (75:25:1)]; *i.e.*, they both had the same R_f (0.40) and matched the major decomposition product seen in the TLC of the spent reaction mixture. Neither A nor B melts below 290°.

Anal.—Calc. for $C_{14}H_{10}ClNO_2$: C, 64.80; H, 3.86; Cl, 13.70; N, 5.41. Found (A): C, 64.74; H, 3.93; Cl, 13.61; N, 5.44; (B): C, 64.71; H, 4.03; Cl, 13.89; N, 5.35.

As seen in Figs. 4 and 5, whereas protons *a*, *b*, and *c* show only small shift differences, a large difference exists between the *d* protons and the remaining protons. In this case, the isomer having protons in the 5,6-positions, *i.e.*, III, would be expected to exhibit a larger shift difference than the isomer having protons in the 6,7-positions, *i.e.*, II. Protons in the 2-, 3-, and 4-positions are common to both structures. Furthermore, the anisotropic effect (3) of this aromatic system would likewise cause the signal arising from the methyl protons in the 5-methyl isomer to be shifted downfield to a greater extent than would the chlorine atom (position 8), which is adjacent to the methyl group in the 7-methyl isomer.

Absorptions characteristic of —NH— and —CO₂H were observed in the IR spectra (KBr dispersion) of both A and B (Table I).

UV spectra were determined in solvents as noted (Figs. 1–3). The UV properties for II, λ_{max} ($\epsilon \times 10^{-3}$), were 355 (7.98), 280 (18.4), and 253 (22.0) nm. For III, λ_{max} ($\epsilon \times 10^{-3}$), they were 351 (7.21), 302 (10.09), 278 (18.90), and 252 (18.65) nm.

The relative amounts of II and III as produced by photolysis were determined from the UV spectrum of the spent reaction mixture, with the assumption that the observed spectrum was the result of significant absorption contribution from only II and III.

Compounds II and III have equal molar absorptivities at 351 nm. whereas at 302 nm. absorptivity differs. The absorbance ratio, $R = A_{\lambda 302}/A_{\lambda 351}$, then reflects relative composition and is independent of concentration. The R values for pure II and III are 0.94 and 1.435, respectively. The fraction of the total carbazole photolysis

Table II—NMR Data^a Obtained for Fractions A and B

Group or Proton	Chemical Shifts, p.p.m. ^b	
	5-Methyl Isomer, II	7-Methyl Isomer, III
CH ₃	2.70	2.50
H-2 ^c	8.27 (d)	8.33 (d)
H-3 ^c	7.30 (t)	7.30 (t)
H-4 ^c	8.05 (d)	8.05 (d)
H-5 ^c	—	7.97 (d)
H-6 ^c	6.96 (d)	7.15 (d)
H-7 ^c	7.37 (d)	—

^a Chemical shifts are in parts per million from external tetramethylsilane; d = doublet, t = triplet. ^b Dimethyl sulfoxide as solvent. ^c Center of multiplet.

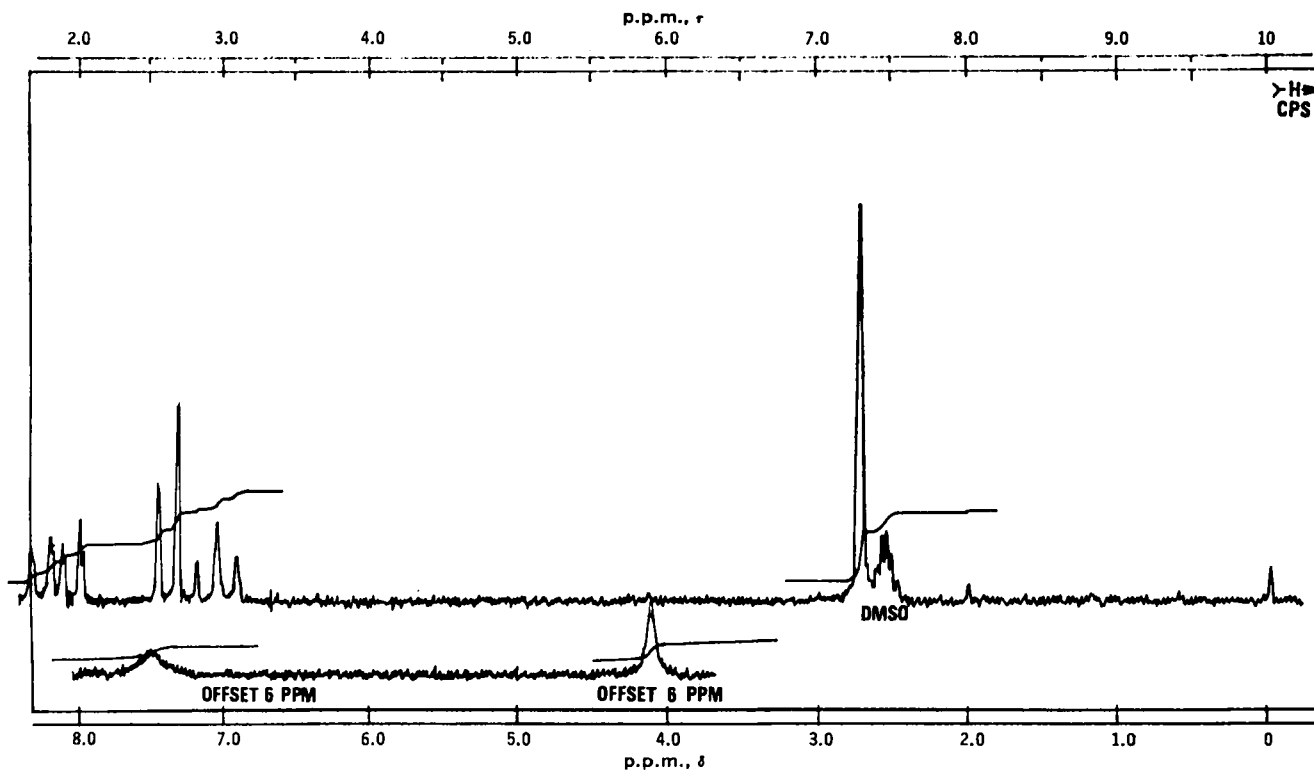
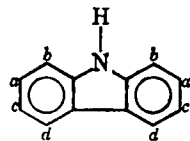


Figure 5—NMR spectrum of II in dimethyl sulfoxide- d_6 . For carbazole (acetone as solvent):



the following assignments are made (τ p.p.m.): a, 7.17; b, about 7.45; c, 7.49; and d, 8.12.

products present as III is calculable from the following equation:

$$f_{III} = \frac{R_{obs} - R_{II}}{R_{III} - R_{II}} \quad (\text{Eq. 1})$$

The value of R_{obs} was 1.175, which then leads to an f_{III} value of 0.475 and an f_{II} value of 0.525. An equimolar mixture would have $f_{II} = f_{III} = 0.50$.

CONCLUSIONS

Irradiation of solutions of *N*-(2,6-dichloro-*m*-tolyl)anthranilic acid results in decomposition to 8-chloro-5-methylcarbazole-1-carboxylic acid and 8-chloro-7-methylcarbazole-1-carboxylic acid (and HCl). The photolysis products are formed in approximately equimolar amounts.

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