Photolysis of 5-Nitrofuramides in Methanol

LARRY J. POWERS

Abstract □ A preliminary investigation of the photolysis of *N*-butyl-5-nitro-2-furamide in methanol is reported. The photolysis product was identified as *N*-butyl-5-methoxy-2-furamide, corresponding to the displacement of the nitro group by a solvent molecule. The nitro group apparently gives rise to nitrite ion, which was qualitatively detected in the photolysis mixture.

Keyphrases □ 5-Nitrofuramides—photolysis in methanol □ Photolysis—5-nitrofuramides in methanol □ *N*-Butyl-5-methoxy-2-furamide—identification as photolysis product

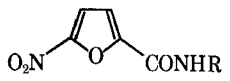
Nitrofuran antibacterial agents undergo two reactions *in vitro*, which have been proposed by various workers to account for their detoxification and/or antibacterial activity *in vivo*. The reduction of the nitro group to a hydroxyl amine has been proposed to be important in both the detoxification (1) and the antibacterial activity (2) of the nitrofurans. The second reaction, which has been observed *in vitro*, is the displacement of the nitro group by a nucleophile. This reaction was proposed by Yoneda and Nitta (3) to account for the antibacterial activity of nitrofurans and by Boyland and Speyer (4) to account for the detoxification of the nitrofurans.

DISCUSSION

As part of an investigation into the antibacterial activity of nitrofurans, the nitrofuramides (I) were synthesized (5). These compounds were previously prepared by Snyder (6) and shown to be approximately as effective *in vitro* as nitrofurazone. Since it was observed that the aliphatic amides decomposed on exposure to light while the aromatic amides were stable, an attempt to isolate and identify the photoproduct of this reaction was undertaken.

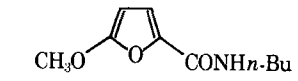
The lack of decomposition in the absence of light was verified using TLC and UV spectroscopy. *N*-Butyl-5-nitro-2-furamide (I*a*) was chosen for the studies aimed at the isolation and identification of the photoproducts because of its adequate solubility and rapid decomposition. Examination of the UV spectrum of the solution of I*a* in methanol and in water before and after photolysis revealed that the nature of the photoproduct was solvent dependent (Fig. 1). Lack of absorption in the UV spectrum above 220 nm. indicates that the photolysis in aqueous solution leads to the destruction of the furan ring (Fig. 1, Curve C). The photolysis of the nitrofuramide in methanol apparently leads to the formation of another furan derivative, as evidenced by the absorption maximum at 283 nm. (Fig. 1, Curve B). For this reason, the reaction in methanol was chosen for this initial investigation of the photolysis reaction.

The nitrofuramide I*a* was dissolved in methanol and stirred under fluorescent lighting in a Pyrex flask for 1 week. Evaporation of the solvent and column chromatography yielded one photoproduct and recovered starting material. The UV spectrum of the isolated photoproduct was as expected from the preliminary observations (Fig. 1, Curve C). The IR spectrum indicated that the amide portion of the molecule was still intact (2.80 and 5.99 μ) but that the nitro group had been lost (lack of absorption at 7.40 μ). In the NMR spectrum, the signals for the butyl protons were as expected. A three-proton singlet at 3.9 δ suggests the presence of a methoxy group. The only other signals in the spectrum were doublets centered at 5.3 and 7.0 δ and a broad singlet at 6.2 δ. These signals were assigned to two furan ring protons and an amide proton, respectively. The coupling constant (3.5 Hz.) of the furan ring protons indicates that the furan ring has 2,5-substitution (7, 8). Based on this evidence, the structure of the photoproduct was assigned as *N*-butyl-5-methoxy-2-furamide (II), corresponding to the displacement of the nitro group by a solvent molecule. The elemental analysis supports this structure, and the UV spectrum ($\lambda_{max.}$ = 283 nm., log ϵ = 4.10) is in good agreement with the UV data reported by Manly and Amstutz (9) for methyl 5-methoxy-2-furoate ($\lambda_{max.}$ = 279 nm., log ϵ = 4.10).



I

Ia: R = *n*-butyl



II

The detection of nitrite ion in the reaction mixture using Ilosvay's diazotization method (10) indicates that the displacement of the nitro group by a solvent molecule is the general pathway to the photoproduct. Boyland and Speyer (4) previously observed that glutathione transferase catalyzes the displacement of the nitro group of nitrofurans as nitrite by glutathione.

If the photolysis of the furamide I*a* in aqueous solution gives rise to a corresponding displacement of the nitro group by a solvent molecule, a 5-hydroxyfuramide would result. Since this 5-hydroxyfuramide would probably enolize and hydrolyze in the aqueous solution, a displacement reaction by a solvent molecule would account for the changes in the UV spectrum of I*a* on photolysis in aqueous solution as well as in methanolic solution. The photodecomposition of the nitrofurans in both aqueous and methanolic solutions is currently being investigated in greater detail in the hope of determining the importance, if any, of displacement reactions in the physiological effects of nitrofurans.

EXPERIMENTAL[1]

***N*-Butyl-5-nitrofuramide**—This compound was synthesized from 5-nitrofuroic acid[2] using the procedure of Snyder (6); m.p. 92–93° [lit. (6) 92.5–93.5°]. The NMR, IR, and UV spectra of the compound were as expected.

Photolysis of *N*-Butyl-5-nitro-2-furamide—I (2.0 g., 0.0093 mole) was dissolved in 50 ml. of methanol, and the solution was stirred in a nitrogen atmosphere for 1 week under fluorescent lighting. The solvent was evaporated, and the residue was chromatographed on silica gel (100 g.) using ether–benzene (10–15% ether) as the eluting solvent system. Early fractions contained unchanged starting material (1.8 g.). Subsequent fractions yielded 0.2 g. of a light-yellow powder, which was recrystallized from hexane–benzene to give light-yellow crystals: m.p. 59–60°; IR (CCl_4): 2.80 μ (N—H), 5.99 μ (C=O), 6.40 μ (N—H + C—N); NMR ($CDCl_3$): 0.7–1.0 (m, 3, CH_3C), 1.1–1.5 (m, 4, CH_2), 3.2–3.5 (m, 2, N—CH_2), 3.9

[1] Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were determined in $CDCl_3$ (tetramethylsilane) solution on a Varian A-60A analytical spectrometer. Resonances are expressed as δ values. IR spectra were determined in CCl_4 solution (0.2 mm.) on a Perkin-Elmer model 137 spectrophotometer. UV spectra were determined on a Perkin-Elmer 202 spectrophotometer. Nitrite ion was qualitatively determined using a standard procedure (10).

[2] Eastern Chemical Co.

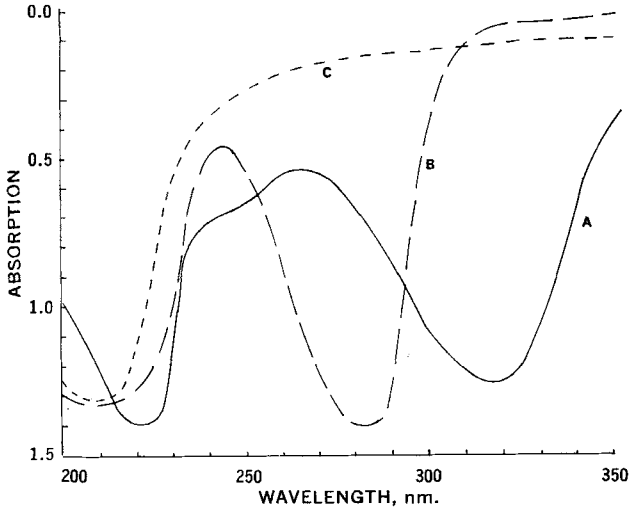


Figure 1—*Changes in UV absorption spectra of aqueous and methanolic solutions of Ia on exposure to light. All solutions are 1 × 10⁻⁴ mole/l. Key: Curve A, UV spectrum of Ia in water prior to exposure to light (the spectrum in methanol is essentially the same); Curve B, methanolic solution after exposure to light for 24 hr.; and Curve C, aqueous solution after exposure to light for 24 hr.*

(s, 3, O—CH_3), 5.3 (d, 1, J = 3.5 Hz., H—C4), 7.0 (d, 1, J = 3.5 Hz., H—C3), and 6.2 (s, 1, N—H).

Anal.—Calc. for $C_{10}H_{15}NO_3$: C, 60.88; H, 7.68; N, 7.10. Found: C, 61.03; H, 7.68; N, 7.07.

REFERENCES

(1) H. E. Paul and M. F. Paul, in "Experimental Chemotherapy," vol. II, Academic, New York, N. Y., 1964, chap. 7.

(2) K. Hirano, S. Yoshina, K. Okamura, and I. Suzuka, *Bull. Chem. Soc. Japan*, **40**, 2229(1967).

(3) F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.*, **12**, 1264 (1964).

(4) E. Boyland and B. E. Speyer, *Biochem. J.*, **119**, 463(1970).

(5) L. J. Powers and G. E. Bass, to be published.

(6) H. R. Snyder, Jr., *J. Med. Chem.*, **10**, 737(1967).

(7) S. Gronowitz, G. Sorlin, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi*, **19**, 483(1962).

(8) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p. 99.

(9) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **22**, 323 (1957).

(10) F. Feigl, "Qualitative Analysis by Spot Tests," 3rd ed., Elsevier, New York, N. Y., 1946, p. 248.

ACKNOWLEDGMENTS AND ADDRESSES

Received March 15, 1971, from the *Department of Molecular and Quantum Biology, College of Pharmacy, University of Tennessee Medical Units, Memphis, TN 38103*

Accepted for publication April 21, 1971.

The author thanks Doctor Frederic C. Chang of this Department for his helpful suggestions during the preparation of this manuscript.

COMMUNICATIONS

Benzene Analogs of Triazenoimidazoles

Keyphrases ☐ Triazenoimidazoles, benzene analogs—synthesis, antileukemic activity ☐ Triazenobenzamides—synthesis, light stability, antileukemic activity ☐ Antileukemic activity—triazenoimidazoles, benzene analogs

Sir:

The fact that 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (I*a*) (NSC-45388) increased survival time in mouse lymphatic leukemia L-1210 and inhibited other neoplasma (1) led to the synthesis of similar triazenoimidazole amides (2–6), triazenoimidazole esters (I*b*) (7), heterocyclic ring analogs (8–11), and certain phenyltriazenes with *para*-attached chains selected for presumed carrier properties (12). Benzene analogs (II–IV) of the triazenoimidazole amides and esters, as well as similar *para*-substituted derivatives (V–VIII), were also synthesized for antineoplastic evaluation; investigations of such derivatives were further stimulated by demonstrations of clinical activity by Compound I*a* (13). This communication is a preliminary account of some of the structural changes made in the aryl moiety and of antileukemic activity by certain of these derivatives.

The *p*-benzamides (V), the *o*- and *p*-benzoates (IV and VII), and the *p*-benzamidines (VIII) were prepared by diazotizing the appropriate aromatic amine derivative and coupling with an aliphatic amine by the general procedure described for certain other phenyltriazenes (12). The *o*- and *p*-benzoic acid hydrazides (III and VI) were obtained by treating the analogous esters (IV and VII) with hydrazine. Since it is well known that diazotization of 2-aminobenzamides gives 1,2,3-benzotriazin-4(3*H*)-ones (14), the *o*-benzamides (II) were synthesized by first isolating *o*-carbamoylbenzenediazonium tetrafluoroborate [m.p. 114–115° dec., IR band at 2290 cm.$^{-1}$ (N_2^+)]. Calc. for $(C_7H_6N_3O)^+BF_4^-$: C, 35.78; H, 2.57; N, 17.88. Found: C, 35.77; H, 2.61; N, 17.75. Coupling with aliphatic amines was then performed in anhydrous media to minimize intramolecular cyclization to 1,2,3-benzo-