PHOTODEGRADATION OF SOLUTIONS OF THE ANTITUMOUR DRUG DTIC

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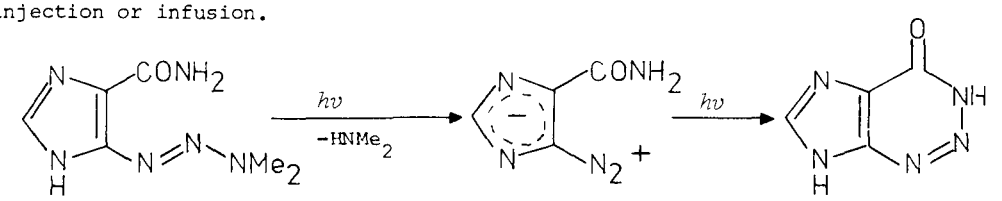
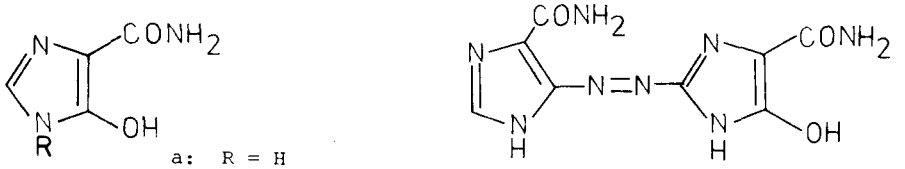
5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC: 1) is used for the treatment of malignant melanoma (Carter & Friedman, 1972). Solutions of pure DTIC are sensitive to light and rapidly photolyse to 5-diazoimidazole-4-carboxamide (Diazo-IC: 2) and thence to 2-azahypoxanthine (3) (Shealy & others, 1961): both these reactive products possess a wide spectrum of biological activity (Stevens, 1976). We have re-examined the photodecomposition of DTIC because of reports from hospital pharmacists that solutions of the drug formulation-DTIC Dome, or dacarbazine - on occasions turn red when prepared for injection or infusion.



(1) (2) (3)

DTIC Dome is the citrate salt of the triazene containing mannitol, and photodegradation of the formulated product differs significantly from that of pure DTIC. A dilute aqueous solution of DTIC Dome (1 mg in 100 ml; λmax 326 nm) is completely transformed within 1 minute to Diazo-IC (λmax 315 nm) in direct sunlight. After 30 minutes there is no further change and the solution contains an absorbing species with λmax 235 and 277 nm (Absorbance 235/277 = 0.47). The new species is *not* 2-azahypoxanthine (λmax 249 and 280 nm; Absorbance 249/280 = 1.2). In contrast a similar concentration of pure Diazo-IC under identical conditions affords only 2-azahypoxanthine: however, when 1 equivalent of citric acid - but not mannitol - is included in the solution the new photoproduct is formed exclusively. This compound has been identified as 5-hydroxyimidazole-4-carboxamide (4a) by comparison of its spectral characteristics with authentic material.



a: R = H
(4) b: R = β-D-ribofuranosyl (5)

Concentrated aqueous solutions of the drug formulation (100 mg in 50 ml) evolve gas and turn red when exposed to sunlight. After 10 hr a maroon solid is formed (20%) and is identified as the azoimidazole (5) since it is identical with the product independently formed by coupling Diazo-IC (2) and the hydroxyimidazole-carboxamide (4a) at pH 7. Apart from reinforcing the warning that DTIC should at all times be protected from light, this new observation that citric acid diverts the photolysis to hitherto unexpected products may be important since the hydroxyimidazole-carboxamide (4a) has recently been identified as the aglycone fragment of the new antitumour antibiotic bredinin (4b) (Sakaguchi & others, 1975).

Carter, S.K. & Friedman, M.A. (1972). *Eur. J. Cancer*, 8, 85-92.
Shealy, Y.F., Struck, R.F. & others (1961). *J. Org. Chem.*, 26, 2396-2401.
Stevens, M.F.G. (1976). *Progr. Medicin. Chem.*, 13, 205-269.
Sakaguchi, K., Tsujino, M. & others (1975). *J. Antibiotics*, 28, 798-803.