entirely reversible; (c) vehicles had no effect on elimination rates; (d) all processes could be described by linear compartment modelling, and (e) contribution of the 'reservoir— effect was negligible.

REFERENCE

BARRY, B. W. & WOODFORD, R. (1974). *Br. J. Derm.*, in the press.

Stability of drugs in the presence of pharmaceutical colours

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Colours are used in pharmaceuticals both for aesthetic value and identification purposes. For the colouring of tablet sugar coats, lakes are coming increasingly popular as they offer advantages over water soluble dyes in speed of application and colour uniformity. Although the colour stability of dyes and lakes has been studied (Goodhart, Lieberman & others, 1967), interaction between colours and drugs has received little attention. The following report deals with the degradation of phenylbutazone in the presence of pharmaceutical lakes.

F.D & C Red 2 Lake (Amaranth), F.D & C Red 3 Lake (Erythrosin), F.D & C Yellow 5 Lake (Tartrazine) and F.S & C Yellow 6 Lake (Sunset Yellow) may be used in combination to give a colour suitable for the sugar coating of phenyl-butazone tablets. Suspensions, in Sorensen's phosphate buffer (pH 7·4), of the individual lakes were prepared and stored in subdued light. Solutions of phenylbutazone were similarly prepared. Mixtures of phenylbutazone and the lakes were exposed, in 1 cm quartz cells, to unfiltered light from a 300 W projector bulb, situated 50 cm from the cell. At various time intervals, the cell was removed from the beam, and the phenylbutazone concentration measured spectrophotometrically at 264 nm. Corrections were applied for absorbance due the lake, and interference from the degradation product (Beckstead, Kaistha & Smith, 1968).

Under the conditions used, phenylbutazone alone, and in the presence of amaranth, tartrazine and sunset yellow was stable. In the presence of erythrosin, degradation of the phenylbutazone occurred, the rate constants for the degradation of a 0·001% solution being dependent on the concentration of lake as shown in Table 1.

Table 1.

Concn of lake* (mg litre^{-1})	1·23	2·45	4·90	9·80
Rate Constant (min^{-1})	0·017	0·019	0·091	0·155

* Dye content of lake = 40% w/w.

The reaction did not occur in the dark. In the presence of water soluble erythrosin dye of equivalent concentration, the reaction still occurred, but was slower. Examination of the degradation product of the reaction by t.l.c. (Awang, Vincent & Matsui, 1973), indicated a single breakdown product, which by comparison with standard reference samples was identified as 1,2-diphenyl-4-n-butyl-4-hydroxyprazolidine-3,5-dione (This product is formed from phenylbutazone by oxidation).

It is well recognized that reactions involving dyes as photosensitizers are often mediated by singlet oxygen (Chapelon, Perichet & Pouyet, 1973). Flushing the cells with nitrogen before exposure reduced the rate of degradation. Methylene blue, a known generator of singlet oxygen, also degraded the phenylbutazone to an identical product.

It is suggested that the degradation of phenylbutazone under the experimental conditions described is due to oxidation by singlet oxygen generated by the erythrosin. The effect is enhanced by laking the dye, perhaps due to adsorption of the drug.

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REFERENCES

AWANG, D. V. C., VINCENT, A. & MATSUI, F. (1973). *J. pharm. Sci.*, **62**, 1673–1676.
BECKSTEAD, H. D., KAISTHA, K. K. & SMITH, S. J. (1968). *Ibid.*, **57**, 1952–1957.
CHAPELON, R., PERICHET, G. & POUYET, B. (1973). *Mol. Photochem.*, **5**, 77–81.
GOODHART, F. W., LIEBERMAN, H. A., MODY, D. S. & NINGER, F. C. (1967). *J. pharm. Sci.*, **56**, 63–67.

Catalytic degradation of hydrocortisone disodium phosphate solutions by copper(II) ions

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As part of a general study of the stability of hydrocortisone 21-phosphate (HDP) solutions, the effect of metal ions has been investigated. Traces of copper profoundly accelerate both the hydrolysis of the 21-phosphate ester linkage and the subsequent oxidative degradation of the dihydroxy-acetone side-chain with significant effects being observed at copper concentrations as low as 0·1 p.p.m. (w.r.t. HDP). The main degradation products are hydrocortisone, 11 β hydroxyandrost-4-ene-3,17-dione, 11 β,17α-dihydroxy-3,20-dione-4-pregnene-21-al, and 11 β, 17α-dihydroxy-3-oxo-4-etienic acid. The formation of the 21-aldehyde, a yellow, substituted glyoxal, is shown to be the cause of the undesirable yellowing of HDP solutions. The compound is known to be readily produced from the 20-keto-21-hydroxy steroid by catalytic concentrations of cupric ions (Lewbart & Mattox, 1963). The products were identified and measured by a combination of two or more of the methods of t.l.c., g.l.c., n.m.r., i.r. and u.v. spectroscopy together with elemental analysis. Copper was determined (at levels as low as 0·01 p.p.m.) by chelation and solvent extraction followed by atomic absorption spectrophotometry. Hydrolysis was measured by determining the inorganic phosphate formed, (Mokrasch, 1961) and the oxidative production of 21-aldehyde assessed from measurements of optical density at 450 nm. The copper-catalysed hydrolysis and oxidation processes are both pseudo-first order with respect to HDP concentration and the activation energy for hydrolysis (measured at 37°, 50°, 70°, 80° and 90°) is 107·0 KJ mol^{-1}. The order of both reactions with respect to copper concentration is 0·28, which strongly suggests that the hydrolysis, as the initial step in the degradation sequence, is rate-determining. No differences were shown between the degradation kinetics of submicellar and supra-micellar concentrations of HDP. The effect of antioxidants, buffers and EDTA will be briefly discussed and mechanisms proposed for the role of copper ions. Of nine ubiquitous metal ions examined, only copper, iron and nickel showed enhancement of degradation at catalytic concentrations. The effects shown by iron and nickel were only about 20 and 8%, respectively, of that produced by copper.

REFERENCES

LEWBART, M. L. & MATTOX, V. R. (1963). *J. org. Chem.*, **28**, 2001–2006.
MOKRASCH, L. C. (1961). *Analyt. Chem.*, **33**, 432–434.

Mechanism of degradation of 5-bromouracil in aqueous solutions of sodium bisulphite

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A kinetic study has been made of the reactions that occurred at 25° in solutions which contained 5-bromouracil (I) (initial concentration range 0·5–1·0 $\times 10^{-2}$ M) and sodium bisulphite (initial concentration range 0·5–6·0 $\times 10^{-1}$ M). Reactions were studied throughout the pH range 4·0–7·5 and ionic strength was maintained at 1·0 M with potassium chloride.

It has previously been reported (Sander & Deyrup, 1972) that uracil (II) was rapidly formed by reactions of I in aqueous sodium bisulphite and that II was slowly converted to