

This Week's Citation Classic

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Nash T. The colorimetric estimation of formaldehyde by means of the Hantzsch reaction. *Biochemical J.* **55**:416-21, 1953. [Air Hygiene Lab., Public Health Laboratory Service, London, England]

A colour reaction for low concentrations of formaldehyde is described which depends on the formation of diacetyl-dihydrolutidine from acetyl-acetone and formaldehyde in the presence of excess ammonium salt. Conditions can be mild enough for the survival of biological material. [The SC[®] indicates that this paper has been cited over 1,340 times since 1961.]

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"I am indebted to Dr. (now Professor Sir Robert) Williams for bringing me into the team [The (British) PHLS Committee on Formaldehyde Disinfection] which investigated the use of formaldehyde for disinfecting fabrics. He gave me the job of finding a non-toxic neutralizing agent with which to treat infected fabric after exposure to formaldehyde vapour, in order that the bacterial viability results should not be invalidated by any bacteriostatic action of residual formaldehyde.

"In the course of this work, which had a fairly successful conclusion,¹ I tested various single compounds and then went on to test two-component mixtures as suggested by a study of Robinson's classical researches into alkaloid synthesis in plants, where formaldehyde is a key intermediate.² In such

reactions, aptly termed 'syntheses under physiological conditions' quite complicated condensations can occur in cold dilute aqueous solution at around neutral pH. Typical of these is the Hantzsch dihydropyridine synthesis by reaction between ammonia or a primary amine, an aldehyde, and two molecules of a beta-diketone or beta-ketoester. I found that the three simplest possible precursors, acetyl-acetone, ammonia, and formaldehyde, gave a coloured product, diacetyl-dihydro-lutidine (DDL). The reaction was of no value as regards the initial aim of the work, but was successfully followed up as a possible basis for a colorimetric method.

"The reagent was particularly useful in the estimation of formaldehyde vapour concentration over diluted commercial formalin, which gives off a non-bactericidal gas (probably methylene dimethyl ether) which reacted as formaldehyde towards, e.g., the chromotropic acid reagent, but was unreactive towards mine. As regards other methods of estimating DDL, its rather weak fluorescence in solution was not important at the time, but with modern instrumentation, fluorimetry is now a feasible alternative.

"DDL is readily obtained pure, and an interesting later development was the use of a saturated aqueous solution (about 100 micromolar) as a selective colorimetric reagent for ozone.³ Working out various possible structures on paper, the ozonolysis product of DDL looks like a promising chelating agent for some metals, but I have not followed this up. The popularity of the Hantzsch reagent is probably due to (1) the spelling, (2) the impeccable century-old pedigree, (3) the fact that it can be spilt about and even imbibed with little harm, in contrast to the hot strong acids or alkalis of other reagents."

1. **Nash T. & Hirsch A.** The revival of formaldehyde-treated bacteria. *J. Appl. Chem.* **4**:458-63, 1954.
2. **Robinson R.** The structural relations of some plant products. *J. Roy. Soc. Arts* **96**:795-808, 948.
3. **Nash T.** Colorimetric determination of ozone by diacetyl-dihydrolutidine. *Atmos. Environ.* **1**:679-87, 1967.