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A Review of the Use of Aqueous Hydrofluoric Acid in the Manufacture of Betamethasone

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Abstract:

For more than 30 years aqueous hydrofluoric acid has been safely used on a manufacturing scale in the synthesis of betamethasone, a medium-activity glucocorticosteroid used in the treatment of various inflammatory disorders. This report describes the requirements of plant design and aspects of safety when using aqueous hydrofluoric acid in routine manufacture.

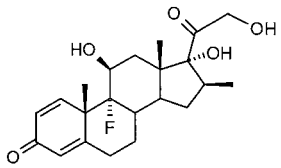

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Figure 1. **Betamethasone alcohol (1).**

Introduction

Hydrofluoric acid (HF) is usually a gas at room temperature with a boiling point of 19.5 °C. The affinity of this acid for water makes it very easy to prepare aqueous solutions of varying strengths. Aqueous HF is generally regarded as a weak acid, being highly undissociated as an ion pair in solution.[1]

The ability of the fluoride ion to extract the silica from glass forming silicon fluoride has allowed HF to be used in glass etching since the 17th century.

More recent industrial uses[2] of hydrofluoric acid include the manufacture of insecticides and fertilizers, control of fermentation, stain removal, leather tanning, welding, manufacture of semiconductors, and pharmaceutical and dye production.

In all of these applications the use of hydrofluoric acid is strictly controlled, and the recognition of the importance of procedures governing storage, transportation and ultimately safe handling is a prerequisite.

The physiological effects of hydrofluoric acid are well-known:[3]

• Eye contact with the gas or liquid will cause irritation and may cause serious damage to the cornea, possibly resulting in permanent blindness or total destruction of the eye.

• Skin contact with the gas will cause irritation and smarting. The concentrated liquid will produce severe, painful burns. Skin contact with dilute solutions may not be immediately painful but will lead to the formation of deep ulcers, several hours after contact.

• Inhalation of low concentrations of the gas or vapour will cause irritation to the mucous membranes of the respiratory tract. Higher concentrations cause severe irritation, difficult, painful breathing, paroxysmal coughing, and damage to the lung tissue leading to pulmonary oedema. Symptoms may be delayed for 24 h or more. Chronic inhalation exposure is reported to cause lung, kidney, and liver damage in animals.

• Repeated doses of small quantities of hydrofluoric acid too small to give rise to immediate toxic effects may cause fluorosis, symptomised by weight loss, malaise, anaemia, leucopenia, discoloration of the teeth, and osteosclerosis.

Even in nonindustrial environments exposure to hydrofluoric acid can occur with similar results; recent reports include exposure involving a man cleaning his paint brushes.[4]

The common method of treatment on a small scale[5] is calcium gluconate gel, which can be applied to small splashes to the skin. However, complete removal of the incidences of potential contamination is the only way to safely use hydrofluoric acid.

In this report we describe the use of aqueous hydrofluoric acid in the manufacturing plant and the requirements of plant design and safety procedures to use it in a safe manner.

Discussion

Betamethasone alcohol (**1**) (Figure 1) is a common intermediate in a number of synthetic glucocorticosteroids.[6] It is also the active pharmaceutical ingredient (API) in the

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(1) Davenport, K. In *Handbook of Reagents for Organic Synthesis: Acidic and Basic Reagents*; Reich, H. J., Rigby J. H., Eds.; John Wiley & Sons: Chichester, West Sussex, UK, 1999; pp 187−190.

(2) Chemical Industries Association. Hydrogen Fluoride Producers and Users Sector Group website. http://www.cia.org.uk/aboutcia/hydrogenfluoride.htm. Accessed March 2002.

(3) Wilkes, G. *eMed. J.* **2001**, *2*, 5 (http://www.emedicine.com/emerg/topic804.htm, accessed June 2002). Bertolini, J. C. Hydrofluoric Acid: A Review of Toxicity. *J. Emerg. Med.* **1992**, *10*, 163−168.

(4) Huisman, L. C.; Teijink, J. A W.; Overbosch, E. H.; Brom, H. L. F. *Lancet* **2001**, *358*, 1510.

(5) *Hydrofluoric Acid Poisoning: Recommendations on First Aid Procedures*; Health and Safety Executive leaflet INDG307: HSE Books, Sudbury, UK, 1999..

(6) Elks, J.; May, P. J.; Weir, N. G. U.S. Patent 3,312,590, 1967; Elks, J.; May, P. J.; Weir, N. G. U.S. Patent 3,312,591, 1967; Phillips, G. H.; English, A. F. Br. Patent 1,391,443, 1975; Herzog, H.; Oliveto, E. P. *Steroids* **1992**, *57*, 617.

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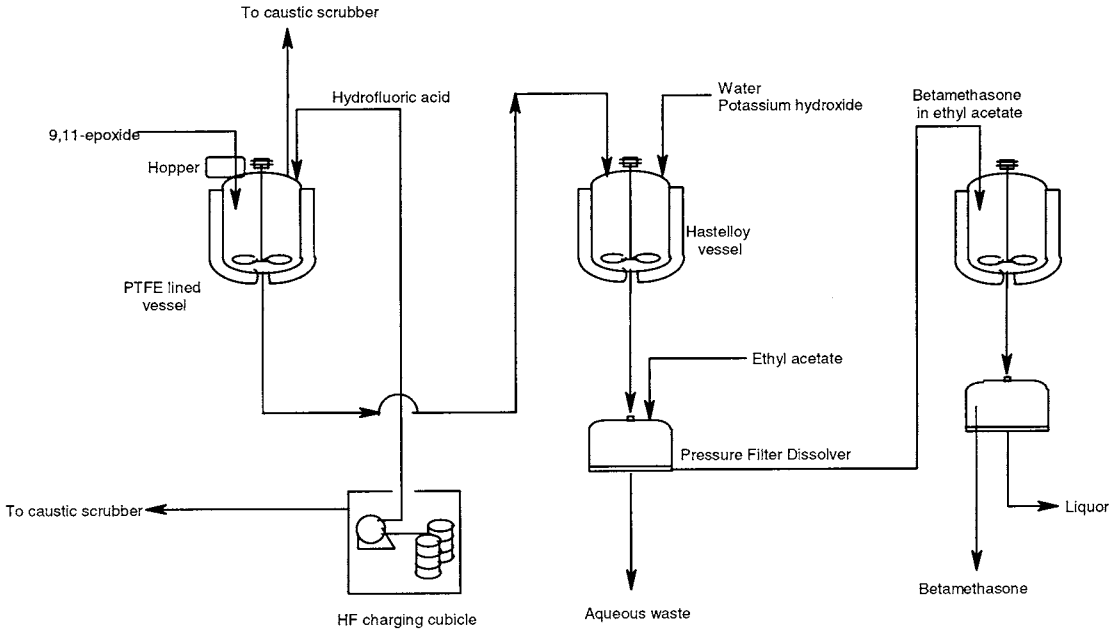
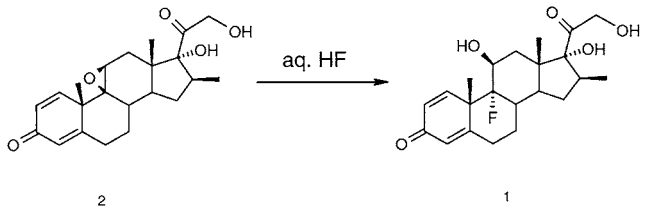


Figure 2. **Manufacturing plant equipment configuration for the synthesis of betamethasone alcohol.**

steroid preparation Betnelan for the treatment of various inflammatory disorders.

Historically, the synthesis of betamethasone within GSK has been carried out using aqueous hydrofluoric acid in a specialised plant, designed to produce ca. 2 tonnes per annum. The reaction itself involves stereospecific ring opening of the 9,11-epoxide intermediate (**2**) as shown below (Scheme 1).

Scheme 1. **Synthesis of betamethasone**



A vast history of literature exists for this and analogous epoxide ring-opening reactions.[7] Few alternatives exist to providing the 9-fluoro-11-hydroxy functionality essential to the glucocorticosteroid's physiological activity, and the cleanliness of the reaction and the relative low price of aqueous HF make it attractive in large-scale synthesis.

Plant-Design Rationale. The plant design had to recognise the characteristics of hydrofluoric acid as well as the requirements of the reaction itself in terms of temperature and other critical parameters. This meant that a glass-lined vessel was certainly not practical.

The main rationale adopted was enclosed handling of the acid and total containment by an interlocked scrubber (potassium hydroxide). The simple plant schematic (Figure 2) shows the general plant configuration; however, embedded safety systems ensure that splashes and spillages are reduced to a minimum.

The aqueous HF is pumped into the PTFE-lined reaction vessel via PTFE-lined pipes. The pipes themselves are shrouded with reactive mufflings, which cover all flanges. The reactive mufflings are pH sensitive and change colour on contact with acid. This pumping operation is further safety linked as the scrubber itself has a high-pressure alarm if the vessel is not extracted to a certain limit, thus avoiding overpressurisation. The vessel also has a high-level alarm, ensuring that no overfilling can take place. The HF cubicle itself stands on a bunded grid, ensuring containment of any spillages for local neutralisation.

Processing Considerations. Limited calorimetric data exists for this reaction; however, heat of formation calculations (on a gas-phase basis)[8] suggest an exotherm of −64.6 kJ/mol. However this is controlled by regulated addition of 9,11-epoxide to the aqueous HF. Thus, the reaction is typically carried out at temperatures below −15 °C, and the jacket has a dedicated low-temperature (−60 °C) heat-transfer fluid.

Charging of the input 9,11-epoxide into the cooled acid is controlled over a fixed period. This is challenging and requires the use of an enclosed vibratory hopper, allowing uniform addition with neither exposure of the process technician to the steroid or HF nor the batch to external contamination.

The workup of the reaction involves drown-out of the batch into water followed by careful pH adjustment using potassium hydroxide to ensure that no HF remains. This is done in a separate Hastelloy vessel. The crude grade material is then filtered and purified by extraction into ethyl acetate followed by crystallisation.

(7) Examples: Hirschmann, R. F.; Miller, R.; Wood, J.; Jones, R. E. *J. Am. Chem. Soc*. **1956**, *78*, 4956; Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1957**, *79*, 1130; Crowe, D. F.; Christie, P. H.; DeGraw, J. I.; Fujiwara, A. N.; Grange, E.; Lim, P.; Tanabe, M.; Cairns, T.; Skelly, G. *Tetrahedron* **1983**, *39*, 19, 3083−3090; see also review: Arkherem, A. A.; Reshetova, I. G.; Titov, Y. A. *Russ. Chem. Rev.* **1965**, *34*, 926.

(8) ΔH_f is calculated by the semiempirical PM3 method at optimised geometries using *Quantum CAChe*, V5.0; Fujitsu Ltd., Japan, 2002.

Specific safety procedures are in place to quickly initiate emergency procedures; these include an alarm to alert the site emergency services and routine health monitoring of process technicians.

Summary

Hydrofluoric acid is a clean reagent that has been handled safely in routine manufacture within GSK for more than 30 years. The manufacturing process for betamethasone has fundamentally changed very little in this time, but still maintains the high standards of safety demanded by such a hazardous reagent.

Acknowledgment

We are grateful to Tony Smith and Bob Harcus for their comments and suggestions and to Mark Wilson for the semiempirical molecular modelling and ΔH_f calculations. This report is dedicated to the process technicians who have ensured ongoing manufacture of betamethasone for more than 30 years.

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