

## The Synthesis of Ethylene-1,2-T Oxide

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Ethylene-1,2-T oxide was synthesized on a vacuum line by the following means: (a) reaction of acetylene and hydrogen-T bromide (obtained from phosphorus pentabromide and water-T) in UV-light to form 1,2-dibromoethane-1,2-T; (b) debromination with Zn to ethylene-1,2-T; (c) reaction with N-bromosuccinimide to form 2-bromoethanol-1,2-T; (d) reaction with KOH to form ethylene-1,2-T oxide. The yield of steps (a) + (b) was *ca.* 100 %, that of (c) + (d) *ca.* 60 %. The product was stored in dibutyl ether from which it could be distilled before use. The radiation chemical stability of this solution was studied.

Ethylene oxide has been found mutagenic in different organisms,<sup>1-3</sup> with a mutagenic efficiency similar to that of ionizing radiations, but definitely inferior in this respect to certain monofunctional alkyl alkanesulfonates.<sup>4</sup> The use of ethylene oxide in chemical industry makes it a possible health hazard; and the occurrence of epoxides in air pollution<sup>5</sup> and, possibly, as radiation chemical products, *e.g.* in irradiated foods<sup>6</sup> increases the desirability of clarifying the uptake and biological reaction mechanisms of the compound.

Quantitative studies of the reaction mechanisms of "radiomimetic" alkylating agents are definitely facilitated by the use of tracer substances tritiated at high specific activities. Since Wilzbach labelling with tritium gas seemed to lead to reaction products (ethanol-2-T and polymers) with the oxirane ring broken,<sup>7</sup> other synthetic procedures were assayed in the present study.

The biological use requires that small samples can be taken from a batch by simple means. The ethylene oxide (b.p. 12°) was therefore kept in a high-boiling solvent, dibutyl ether (b.p. 142°), from which it could easily be distilled before use. Considering the liability to polymerization of ethylene oxide, the radiation chemical stability of its dibutyl ether solution was determined.

A synthesis of ethylene-1,2-T oxide of low specific activity has been described previously,<sup>8</sup> but the yield was low (*ca.* 25 to 35 % on water-T). In the present synthesis, performed on a vacuum manifold, ethylene-1,2-T oxide was obtained in 53% yield from water-T at a specific activity of 90 mCi mmole<sup>-1</sup>.

A mixture of 1 part acetylene and 2 parts hydrogen-T bromide, obtained by reacting water-T with phosphorus pentabromide, was irradiated with ultraviolet light and the addition product under these circumstances,<sup>9</sup> 1,2-dibromoethane-1,2-T, was debrominated with zinc dust to give ethylene-1,2-T. On shaking ethylene-1,2-T with a suspension of N-bromosuccinimide in water containing a little sulfuric acid, 2-bromoethanol-1,2-T was obtained which yielded ethylene-1,2-T oxide upon reaction with potassium hydroxide. Previous syntheses of inactive ethylene oxide carried out in this way had given a product shown to be pure according to gas chromatography.

### EXPERIMENTAL

*Ethylene-1,2-T oxide.* The synthesis was carried out on a vacuum manifold<sup>10</sup> at a pressure of  $10^{-4}$  mm Hg (oil pump backing a mercury vapour diffusion pump fitted with a mercury vapour trap).

Water-T ( $3.52$  mmole at  $90$  mCi mmole<sup>-1</sup>) was distilled on the vacuum line into a  $50$  ml flask (Fig. 1:A) fitted with a tap and containing phosphorus pentabromide ( $1.5$  g,  $3.49$  mmole), the flask being cooled in liquid air. The hydrogen-T bromide formed was condensed into a tared  $250$  ml flask (B) fitted with a tap and attached to the vacuum line, the flask being cooled in liquid air. A trap (C) cooled to  $-78^\circ$  was placed between the vacuum line and the reaction flask and unreacted water-T was distilled from the trap back into the reaction flask from time to time. Yield of hydrogen-T bromide  $557$  mg,  $6.88$  mmole,  $97.8\%$  on water-T.

The hydrogen-T bromide was condensed into a second  $250$  ml flask (instead of B in the figure) fitted with a tap and containing acetylene ( $89.9$  mg,  $3.45$  mmole), the flask being cooled to  $-180^\circ$ . The tap was closed and the flask removed from the vacuum line and irradiated with ultraviolet light for  $24$  h. After reattaching the flask to the vacuum line, the contents were distilled into a trap at  $-180^\circ$  which was then warmed to  $-78^\circ$  and unreacted acetylene and hydrogen-T bromide condensed back into the reaction flask and irradiated for a further  $12$  h. This procedure was repeated. Final yield of 1,2-dibromoethane-1,2-T  $614$  mg,  $3.27$  mmole, *i.e.*  $94.9\%$  on hydrogen-T bromide.

1,2-Dibromoethane-1,2-T was then distilled into a  $50$  ml flask fitted with a tap and containing  $0.6$  ml purified dioxane, zinc dust ( $677$  mg,  $10.2$  mmole), a drop of water and a sodium iodide crystal as well as a magnetic stirrer bead, the flask being cooled in liquid air. The tap was closed and the contents of the flask stirred magnetically on allowing

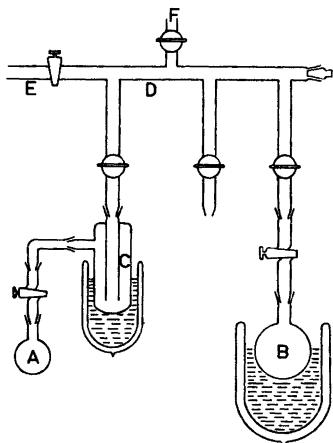


Fig. 1. Detail of apparatus (*cf.* Ref. 10) used for synthesis of hydrogen-T bromide. A,  $50$  ml flask containing phosphorus pentabromide and water-T; B,  $250$  ml flask cooled in liquid air for collection of hydrogen-T bromide; C, Trap cooled in dry ice/acetone to condense unreacted water-T; D, Vacuum line; E, To pumps; F, To manometer.

to attain room temperature. Ethylene-1,2-T was evolved and condensed into a tared 100 ml flask (A in the figure) fitted with a tap and attached to the vacuum line *via* a trap (C) cooled to  $-78^{\circ}$ , the tared flask being cooled to  $-180^{\circ}$ . Material condensed in the trap was distilled back into the reaction flask from time to time and allowed to react again. Yield of ethylene-1,2-T 96.3 mg, 3.43 mmole, *i.e.* 105.1 % on 1,2-dibromoethane-1,2-T.

A 100 ml flask (position B) containing a suspension of N-bromosuccinimide (1.578 g, 6.98 mmole) in 3.5 ml water and 0.5 ml 4 N sulfuric acid was fitted with a tap and attached to the vacuum line and after cooling to  $-180^{\circ}$ , the ethylene-1,2-T was condensed into it. The tap was then closed, the flask removed from the vacuum line and shaken mechanically for 24 h. The flask was reattached to the vacuum line, cooled to  $-78^{\circ}$  and any unreacted ethylene-1,2-T condensed into a flask at  $-180^{\circ}$ . The remaining solution of 2-bromoethanol-1,2-T in water was melted and distilled at room temperature into a 50 ml flask fitted with a tap and attached to the vacuum line, the flask containing potassium hydroxide pellets (4.13 g, 73 mmole) and being cooled in liquid air. The flask was then allowed to warm up and as the solution melted, it was stirred magnetically and the ethylene-1,2-T oxide evolved was condensed into a tared tap-flask (position A) at  $-180^{\circ}$  *via* a trap at  $-40^{\circ}$ . The contents of the trap were distilled back into the reaction flask from time to time and allowed to react again. Yield of ethylene-1,2-T oxide 82.5 mg, 1.87 mmole, *i.e.* 57.3 % on 1,2-dibromoethane-1,2-T, 53.2 % on water-T. This corresponds to a total activity of 168 mCi. The ethylene-1,2-T oxide was kept as a 1 % solution in dibutyl ether under argon in a sealed tube.

*Gas chromatographic analysis of ethylene oxide.* This was performed on a Perkin-Elmer "Fraktometer 116" with a hot-wire detector, using a 20 % polyethylene glycol on Carbowax column. At a column temperature of  $65^{\circ}$  and a helium flow rate of  $36 \text{ ml min}^{-1}$ , the retention time for ethylene oxide was  $2 \frac{1}{4} \text{ min}$ . Inactive syntheses by the described method gave a product which proved to be pure ethylene oxide.

*Radiation chemical stability of ethylene oxide in dibutyl ether solution.* The specific activity of the ethylene-1,2-T oxide prepared was  $90 \text{ mCi mmole}^{-1}$ , *i.e.*  $2.0 \text{ Ci g}^{-1}$ , assuming no loss of specific activity *en route*. Pure ethylene-T oxide of this specific activity will be self-irradiated at a dose rate  $5.8 \times 10^5 \text{ rad day}^{-1}$  by the  $\beta$ -decay of tritium, and a 1 % solution will be exposed to 1 % of this dose rate.

Model experiments were performed using a  $^{60}\text{Co}$  source giving  $300\,000 \text{ rad h}^{-1}$ ; *i.e.* 1 h and 20 h irradiation by this source corresponds to the radiation chemical effect of storage of the 1 % solution for 50 and 1000 days, respectively. (The influence of the difference in linear energy transfer of T  $\beta$ -radiation and  $^{60}\text{Co}$   $\gamma$ -radiation cannot be expected to be great.)

5 ml samples of *ca.* 1 % solutions were  $\gamma$ -irradiated for 1 and 20 h, respectively, the samples being contained in stoppered Pyrex tubes under air as well as under argon. Ethylene oxide was determined by addition of excess 0.2 N HCl in dioxane and back titration with 0.1 N methanolic NaOH.<sup>11</sup>

The decomposition of ethylene oxide was negligible at the lower irradiation dose. After 20 h irradiation, giving  $6 \times 10^6 \text{ rad}$ , a 1.05 % (w/w) solution exhibited the following decrease in ethylene oxide concentration:

under argon:	19.8 %
in air:	25.6 %

These values are not significantly different.

Upon an average, the radiation chemical destruction of one molecule of ethylene oxide requires a dose of *ca.* 11 eV which corresponds to a G-value of *ca.* 9. If we allow 5 % loss of tritiated ethylene oxide due to radiation chemical decomposition, a 1 % solution in dibutyl ether may thus be stored for *ca.* 200 days at a specific activity of  $100 \text{ mCi mmole}^{-1}$ , or for *ca.* 20 days at  $1 \text{ Ci mmole}^{-1}$ , *etc.* These data are valid at the experimental temperature  $25^{\circ}$ .

The high G-value indicates that if chain reactions are not involved, the chief radiation chemical event occurring in the solution of tritiated ethylene oxide consists in the decomposition of this compound in indirect reactions of reactive species from the solvent. An increased stability of the solution at high specific activities would therefore require other measures than dilution, such as change of solvent or decrease of temperature.

*Decomposition products.* A gas chromatographic analysis of the irradiated ethylene oxide in dibutyl ether solution (20 h irradiation) was carried out using a 2,2'-dicyano-

ethoxyethane column at 70° with a He flow rate of 48 ml min<sup>-1</sup>. No volatile decomposition products were detected; for instance there was no detectable peak for dioxane.

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