

at any one time. When mice are painted on the flanks with single applications of benzpyrene, the yield of tumours is affected by the condition of the hair at the time of painting, but because the spread of the new coat is very easily disturbed, for example, by plucking the hair or even by clipping it, controlled conditions are difficult to maintain. This confirms Haddow's finding that coat change is easily disturbed.

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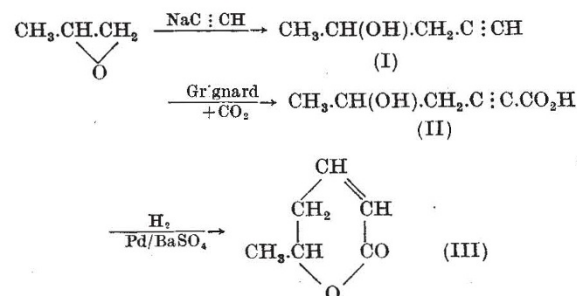
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¹ *Nature*, **155**, 379 (1945).

Synthesis of the Differential Growth Inhibitor, δ -Hexenolactone

Two years ago, Medawar, Robinson and Robinson¹ described the isolation from a commercial malt extract of small quantities of a steam-volatile substance which inhibited the growth of fibroblasts and other mesenchyme cells at concentrations which permitted the free growth of epithelial tissue. It seemed probable that this material was an unsaturated lactone, $C_6H_8O_2$, and it was found that synthetic specimens of *dl*- δ - $\Delta^{\alpha\beta}$ -hexenolactone (III) (the *d*-form of which occurs in the fruit of the mountain ash) exhibited similar inhibitory properties, although the activity was rather less than that of the natural inhibitor. The differential growth-inhibitory properties of this lactone have since been confirmed by other workers².

The *dl*-lactone (III) was synthesized in small yield by Medawar, Robinson and Robinson by condensation of acetaldo with malonic acid in pyridine solution, and Kuhn and Jerchel³ obtained it from β : δ -dibromocaproic acid by boiling with water, the overall yield from sorbic acid being about 25 per cent. We have now found that the lactone can be prepared readily as follows:



Condensation of propylene oxide with sodium acetylide in liquid ammonia gives the carbinol (I) in 50 per cent yield. Treatment of the carbinol with two equivalents of ethylmagnesium bromide followed by carboxylation with carbon dioxide under pressure results in a 75 per cent yield of the crystalline hydroxy-acetylenic acid (II), m.p. 59°, which on semihydrogenation employing a 0.3 per cent palladium-barium sulphate catalyst gives *dl*- δ - $\Delta^{\alpha\beta}$ -hexenolactone directly, as a colourless stable oil, the overall yield from propylene oxide being about 35 per cent. The constants of the lactone are in agreement with those recorded by Kuhn and Jerchel³, and it exhibits the expected growth-inhibitory action*.

* We are indebted to Sir Robert Robinson and Dr. Medawar for a report on the inhibitory properties.

This synthesis has the advantage of being readily adaptable to the preparation of related lactones, and these lines are being actively pursued.

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¹ *Nature*, **151**, 195 (1943).

² Kuhn, Jerchel, Moewus, Moller and Lettre, *Naturwiss.*, **31**, 468 (1943); Hauschka, T. S., *Nature*, **154**, 769 (1944).

³ *Ber. Chem. Ges.*, **76**, 413 (1943).

Metabolism of Quinine in Chick Livers

In a recent paper Oldham, Kelsey, Cantrell and Geiling¹ reported that in White Leghorn chicks dosed with quinine the concentrations of alkaloid in the tissues were lower in young chicks than in grown birds. They suggested that quinine was metabolized more rapidly in chicks than in older birds. *In vitro* experiments by these workers on the quinine oxidase activity of the tissues, however, failed to show any activity in the liver, and showed only very slight activity in the kidney.

In similar experiments on quinine oxidase activity, we have been able consistently to demonstrate definite activity in chick livers (strain: Rhode Island Red \times Light Sussex). Moreover, the activity decreased with increasing age, as shown in the accompanying table. Chick embryo livers and whole embryos show a very high activity.

Material	Mean quantity of quinine (micrograms) metabolized in 2 hours by 0.5 gm. tissue
Whole embryo (10 day) (wt. unknown)	7.0
Embryo liver (10 day)	216
Embryo (20 day)	154
Chick (1 day old)	87
" (1 week old)	97
" (2 weeks old)	69
" (4 weeks old)	94
Chicken (8 weeks old)	53
" (17 weeks old)	45
" (26 weeks old)	19
" (3 years old)	26

The discrepancy between our observations and those of Oldham *et al.* might be partly due to the fact that we used the phosphate buffered salt solution of Krebs and Henseleit² instead of ordinary Ringer-Locke solution, and also raised the temperature of incubation to 40° C. to correspond with the body temperature of the birds. In one experiment on the liver from a three-week old chick in Ringer-Locke, only 30 micrograms of quinine were metabolized. Other causes of the difference of results might be differences in the strain of birds used, or dietary variations. We have in some cases experienced large variations in the quinine oxidase activity among birds of similar age.

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¹ Oldham, F. K., Kelsey, F. E., Cantrell, W., and Geiling, E. M. K., *J. Pharm. and Exp. Therap.*, **82**, 349 (1944).

² Krebs, H. A., and Henseleit, K., *Z. physiol. Chem.*, **210**, 33 (1932).