

Total Synthesis of Vitamins

PALLADIUM CATALYST IN THE MANUFACTURE OF VITAMIN A AND OTHER NATURAL PRODUCTS

A new Hoffmann-La Roche plant at Nutley, New Jersey, which recently started production is to make pseudoionone, a key intermediate in the synthesis of vitamins A and E and β -carotene, from acetone and acetylene. Previous syntheses of these substances have been only partial, starting from citral extracted from lemon-grass oil. The new total synthesis obviates the previous dependence on nature and ensures a stable price and regular source of these products.

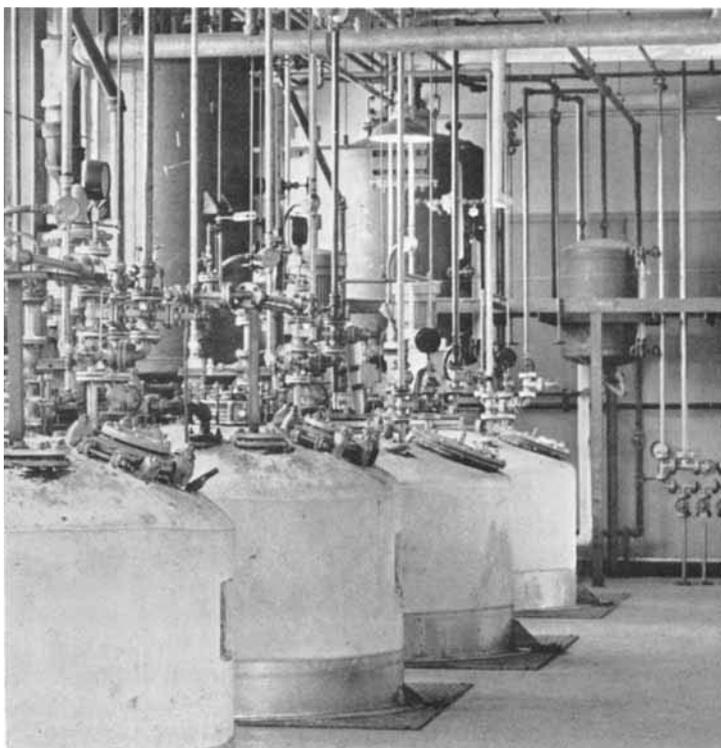
Development of a Continuous Process

The manufacture of diketene is the keystone of the new process. This compound has been little used previously as a chemical intermediate because it is both extremely

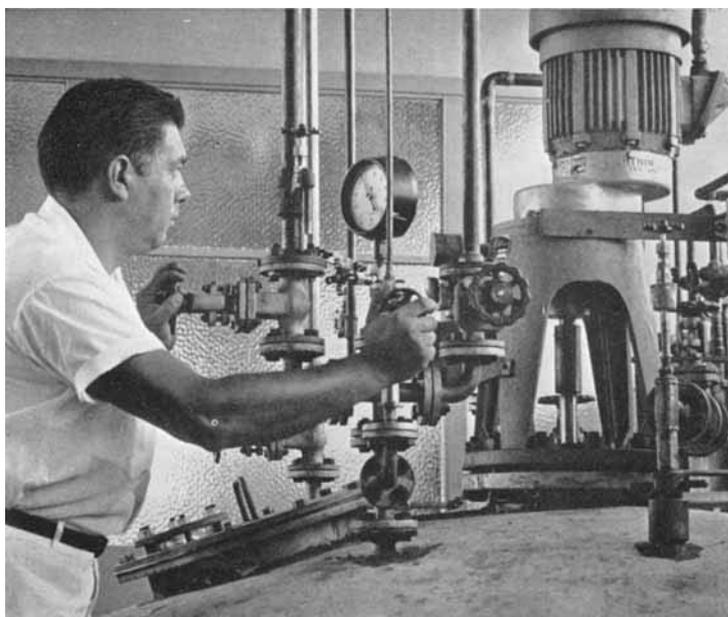
toxic and unstable, so that it provides a most difficult handling problem. By careful engineering design and elaborate instrumentation, however, Roche have evolved a satisfactory continuous process in which acetylene is cracked to ketene and methane; the ketene is autocatalytically dimerised and fractionated.

The entire synthesis is a repetition of three steps in sequence; the ethynylation of the ketone to the tertiary alcohol, hydrogenation of the alcohol to reduce the triple bond, and finally condensation of the alcohol with diketene to form a methyl ketone. Pseudoionone is the product of two such cycles.

The reaction between sodium acetylide and acetone is carried out in liquid ammonia in specially designed reactors adapted for



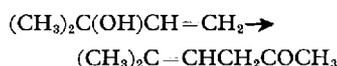
Hydrogenation equipment in the new Roche citral-vitamin A plant, in which a palladium catalyst is employed



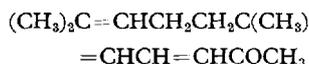
All stages except the production of diketene are carried out in batch equipment. The operator is controlling the hydrogenation of the triple-bond alcohol with Lindlar catalyst

low temperature, low pressure reactions. Subsequent ethynylations are carried out in the same equipment. The resulting product, methylbutynol, is subjected to selective catalytic hydrogenation to form methylbutenol (dimethylvinylcarbinol). The catalyst used is Roche's patented Lindlar catalyst; this is palladium on calcium carbonate, poisoned with lead to the extent that it selectively hydrogenates triple to double bonds without attacking the other points of unsaturation.

The next stage involves a reaction between methylbutenol and diketene followed by pyrolysis to give methylheptenone:



The cycle of reactions is then repeated; in this case the ketone methylheptenone is reacted with acetylene. The higher ketone derived from the second cycle is pseudoionone:



This is separated by distillation. The yield is 35 per cent of the theoretical product of the original acetone and acetylene. From

this compound vitamin E and β -ionone can be prepared directly and from the latter vitamin A and β -carotene can be obtained.

In addition to these products a whole series of terpene derivatives used in flavouring and perfumery can be prepared. Among these are citral, linalyl alcohol, linalyl esters, nerol, irone and many new compounds not now available. A further source of potential development is in building up substituted isoprene chains. For instance synthetic carotene homologues have been prepared which exhibit considerable biological activity.

The process was developed from the laboratory through to complete full-scale production in only six years.

For the initial acetylene-acetone reaction and subsequent ethynylations there are five interchangeable reactors in separate explosion-proof stalls. The hydrogenation stages are conducted in conventional agitated pressure vessels.

Because of the relatively low profit margin of the process, initial operation had to be on the largest possible scale, and a very strong design team was assembled to engineer this unconventional synthesis.