Platinum and Palladium in the Pharmaceutical Industry

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Without question the most important application of platinum and palladium in the pharmaceutical industry is in catalytic hydrogenation. Indeed these two noble metals are frequently the catalysts of choice. Their popularity is largely explained by the rather unique nature of chemical processing operations in this industry.

Production of a pharmaceutical product is usually expressed in pounds per year; in most other sectors of the chemical industry, production in terms of tons per year is the rule. Furthermore, pharmaceutical companies usually market a diversity of products each produced in comparatively small amounts. Relatively small, batchwise operations are, therefore, most common, and the use of standardised low cost, batch process equipment is highly desirable.

Low Pressure Hydrogenation

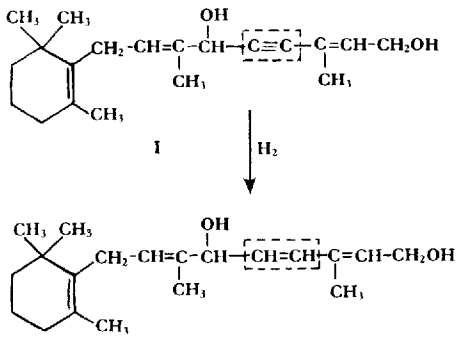
Such equipment is usually rated for use at internal pressures of only one or two atmospheres. In terms of catalytic hydrogenation this means that considerable time and effort are justified in finding conditions whereby a given catalytic reduction may be carried out at a relatively low pressure. Rarely is the anticipated production of a pharmaceutical product sufficient to warrant the much greater capital investment required for the equipment to carry out a catalytic reduction at high pressure. In the few instances where high pressure conditions are required, the catalyst may or may not be a noble metal depending on the type of compound being reduced.

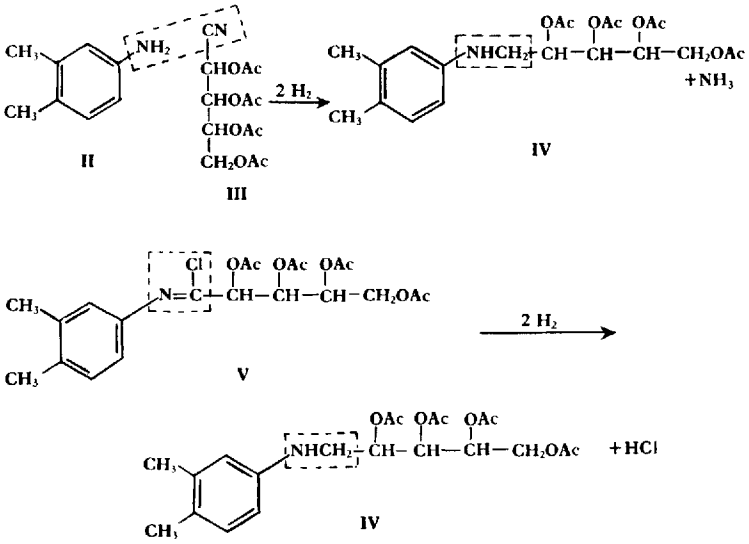
As a consequence of this emphasis on low pressure conditions, platinum and palladium catalysts are the ones most frequently employed because of their outstanding activity in the reduction of a wide range of functional groups at low hydrogen pressure. Other metals, particularly nickel, rhodium and ruthenium, are used to a lesser extent.

Since representatives of practically every class of organic compounds are to be found among known biologically active substances, it is not surprising that catalytic hydrogenations in pharmaceutical processing likewise extend over a wide range of organic compounds and reducible functional groups. Perhaps the best way to indicate the versatility of platinum and palladium catalysts is to cite a few examples of industrial pharmaceutical processes which involve catalytic hydrogenation.

Synthesis of Vitamin A

A key step in an industrial synthesis of Vitamin A is the selective reduction of an acetylenic bond to an olefinic bond in a highly unsaturated intermediate, 1,6-dihydroxy-3, 7-dimethyl-9-(2′,6′,6′-trimethylcyclohexenyl)-2,7-nonadiene-4-yne(I):





Important to the successful accomplishment of this step was the development of a special palladium catalyst supported on calcium carbonate and poisoned with lead acetate and quinoline (1).

The hydrogenation can be carried out either at atmospheric or slightly higher pressure, and is highly selective in adding one mole of hydrogen to the acetylenic linkage without attacking the olefinic bonds.

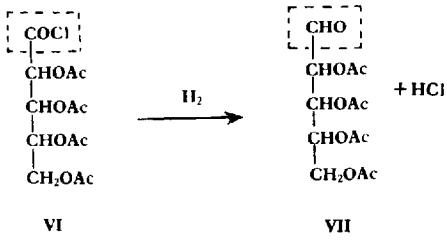
The catalyst has proved useful in the selective reduction of quite a number of acetylenic compounds in addition to the one described above.

Vitamin B_2-Riboflavin

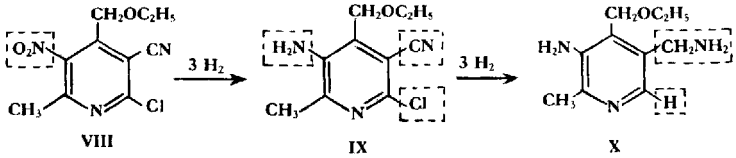
An intermediate common to several industrial processes for manufacturing riboflavin is N-D-ribityl-3,4-dimethylaniline or its tetraacetate (IV). Most, if not all, of these processes involve a catalytic hydrogenation step in the route to this important intermediate. One such catalytic hydrogenation (2) is the reductive coupling of tetraacetyl-D-ribononitrile (III) with 3,4-dimethylaniline (II). This reaction proceeds in the presence of a palladium catalyst at low pressure.

Another published process (3) for preparing the same compound also starts with 3,4-dimethylaniline (II) but employs D-ribonolactone in place of the more difficultly prepared ribononitrile. The initial reaction gives the ribonamide which is acetylated and then dehydrated and chlorinated with phosphorous pentachloride to form the chloroimine (V). The chloroimine (V) is next hydrogenated in the presence of a palladium on calcium carbonate catalyst.

Still another approach (4) to the same intermediate involves the preparation of 2,3,4,5-tetraacetyl-D-ribose (VII) by means of a Rosenmund reduction of tetraacetyl-D-ribonyl chloride (VI) with a palladium on barium sulphate catalyst in refluxing xylene at atmospheric pressure:



The tetraacetyl-D-ribose (VII) is then reductively coupled with 3,4-dimethylaniline, again at low pressure, in the presence of a platinum or palladium catalyst.



VIII IX X

Vitamin B_6-Pyridoxine

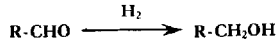
A reported industrial synthesis (5) of pyridoxine, 5-hydroxy-6-methyl-3,4-pyridinedimethanol, employs a stepwise hydrogenation of 2-methyl-3-nitro-4-ethoxymethyl-5-cyano-6-chloropyridine (VIII).

In the first step of the above process, the 3-nitro group is reduced to the amino compound (IX) in the presence of Adam's platinum oxide catalyst. The subsequent step, carried out in the presence of a mixed platinum-palladium catalyst, removes the 6-chloro group by hydrogenolysis and reduces the 5-cyano group to an aminomethyl group. The product (X) is then converted in later steps to pyridoxine by diazotisation and acid hydrolysis.

Outside of the vitamin field there are many other types of pharmaceutical products whose production depends on efficient low pressure catalytic hydrogenations, for example:

Dihydrostreptomycin

One of the earliest isolated and still one of the most useful antibiotics, streptomycin (XI), occasionally produces an allergic reaction in patients who have become sensitised to the drug. The sugar portion of the streptomycin molecule contains a free aldehyde group. It was found that when this aldehyde group is reduced to an alcohol by catalytic hydrogenation in the presence of platinum (6), the resulting dihydrostreptomycin (XII) is fully as active as the parent antibiotic, and can usually be given to patients who have become sensitive to streptomycin itself without producing the allergic reaction:

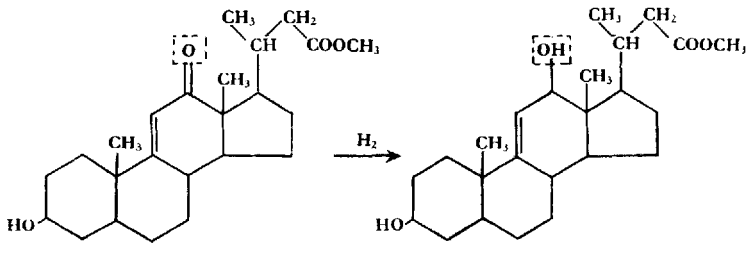


XI XII

where R represents the remainder of the complex streptomycin molecule.

Cortisone

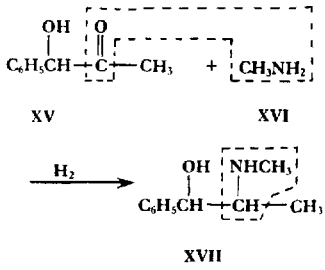
A reported process for manufacturing this valuable drug from bile acids involves a catalytic reduction in a key step shown below. In this reduction, carried out at low pressure in the presence of a platinum catalyst (7), the 12-keto group in compound (XIII) is reduced to a secondary alcohol (XIV). The double bond at position 9,11 is so sterically hindered that under the conditions used it is not reduced.



XIII XIV

Ephedrine

This ancient drug once produced by extraction of the Chinese plant, Ma Huang, is now made synthetically. The Neuberg fermentation process yields the optically active ketol (XV) which will undergo a stereospecific reductive amination with methylamine (XVI) in the presence of a platinum catalyst (8) to give l-ephedrine (XVII).



Another noteworthy feature of using platinum or palladium catalysts is the ease with which they can be recovered from a process economically and practically quantitatively.

Certainly the above examples should suffice to show the versatility and usefulness of low pressure hydrogenation reactions employing platinum and palladium catalysts.

References

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5	S. A. Harris	Ethers of Vitamin B_6. U.S. Patent 2,382,876 (1945)
6	R. L. Peck	Dihydrostreptomycin and Acid Addition Salts. U.S. Patent 2,498,574 (1950)
7	J. S. Lawhead, R. Mozingo and J. van de Kamp	Reduction of 12-Ketosteroids to 12-Hydroxysteroids. U.S. Patent 2,538,109 (1951)
8	G. Hildebrandt and W. Klavehn	Manufacture of Laevo-1-phenyl-2-methylaminopropanol-1. U.S. Patent 1,956,950 (1934)

Platinum Catalyst in Butane Isomerisation

A new process has been developed by Universal Oil Products Company for the economical conversion of normal butane to isobutane, required in increasing quantities as a component of alkylation plant feed stock with the growing use of alkylate for blending into high-octane motor spirit.

In developing this new conversion process, known as the Butamer process, the primary objective was the development of a stable and rugged catalyst capable of operating at relatively low temperatures. In this way the concentration of isobutane in the reactor effluent could be maintained sufficiently high to eliminate an excessive amount of recycle of normal butane. The object has been achieved by the use of a specially prepared platinum-bearing catalyst of high activity which makes it possible to operate the process at economical liquid hourly space velocities, thus providing for a reasonable catalyst inventory. The usual impurities that may be expected in commercial operations act only as temporary suppressors of catalyst activity and the process design may be readily arranged to eliminate any such materials.