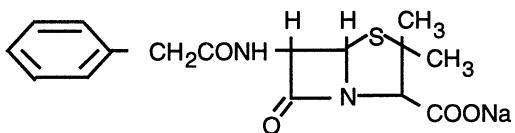


Sodium penicillin G



Penicillin V

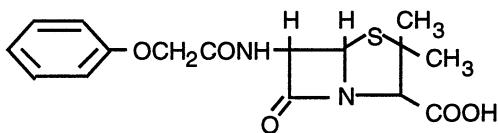


Figure A.4. Chemical structure of penicillins G and V.

Sodium penicillin G (MW = 356.4 KDa, Activity: 1,670 U/mg) is administered parenterally, as it is degraded in acid conditions; penicillin V (MW = 372.4 KDa, Activity: 1,595 U/mg) is acid stable and is orally administered. Both forms are active against Gram positive bacteria by inhibition of cell wall synthesis. Different species of the genus *Penicillium* produce different forms of penicillin. The strain used by Fleming was *P. notatum*. Later on, different strains were used, such as *P. chrysogenum*, which is the most widely used strain in industry. Before utilization in industrial scale, considerable efforts must be spent in strain selection and development to improve the yield and activity of penicillin formation. Selected strains are stored in the form of lyophilized spores. Vegetative cells may be frozen at -70°C with glycerol as a suspending medium.

*P. chrysogenum* can use a variety of carbohydrates and oils as carbon and energy sources. Among those are glucose, sucrose, hydrolyzed starch, lactose, and molasses. Corn oil supplemented with lactose results in fast production of highly concentrated penicillin. Medium formulation has changed significantly with new developments. The original medium (1945) contained the following compounds: lactose, 3–4%; corn steep liquor, 4%; CaCO<sub>3</sub>, 1%; KH<sub>2</sub>PO<sub>4</sub>, 0.4%; antifoam, 0.25%. Improved media resulting in higher penicillin yields have been developed. A typical composition of such media is: glucose or molasses, 10%; corn steep liquor solids, 4–5%; phenylacetic acid (continuous feed), 0.5–0.8% total; vegetable oil-antifoam, 0.5% total.

Corn steep liquor (CSL) is used as a nitrogen source, since it results in higher penicillin yields as compared to the other nitrogen sources. Some compounds in CSL are converted to phenylacetic acid or other side-chain precursors. Cottonseed flour or soybean meal may also be used as nitrogen sources; however, they are more expensive than CSL. Continuous addition of ammonium sulfate to keep the ammonium concentration around 250–300 mg/l is required for continued synthesis of penicillin and to avoid lysis of the mycelium.

Certain precursors of the penicillin side chain need to be added into the fermentation medium. This constitutes a major cost item. Penicillin G requires 0.47 g sodium phenylacetate and penicillin V 0.5 g sodium phenoxyacetate per gram of penicillin produced. Those precursors are fed continuously to avoid possible toxic effects. More than 90% of the precursors are incorporated into the structure of penicillin. Phosphorus supplied by CSL is usually sufficient, since phosphate concentration should be limiting (200–300 mg/l) in the media for penicillin production.

Penicillin is a secondary metabolite with a nongrowth-associated production. The process to produce penicillin involves an initial batch phase in which cell growth occurs. In