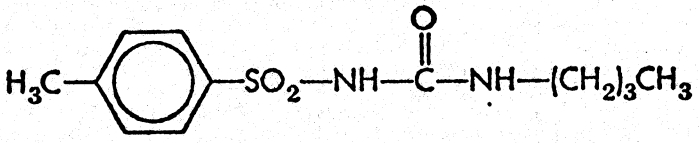
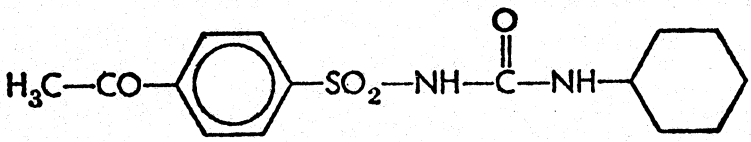
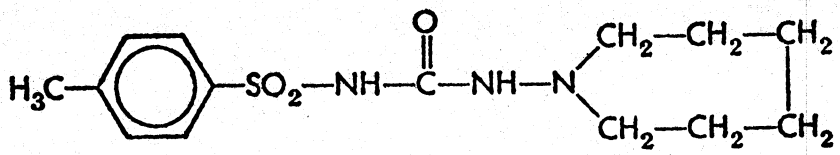


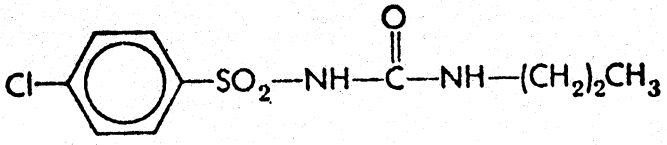
Tolbutamide



Acetohexamide



Tolazamide



Chlorpropamide

All of the effective compounds are arylsulfonylureas with substitutions on the benzene and the urea groups. In the case of tolbutamide, the aryl group is tolyl and the urea substitution is butyl. Tolbutamide differs from the antibacterial compound carbutamide in having methyl instead of amino on the benzene ring. This substitution accounts for the loss of antibacterial properties and for the reduction of toxicity.

Mechanism of Action. The sulfonylureas stimulate the islet tissue to secrete insulin. The evidence, coming as it does from a variety of experimental and clinical studies, unequivocally supports such a conclusion. Administration of sulfonylureas increases the concentration of insulin in the pancreatic vein in cross-circulation experiments. Recipient animals, diabetic or nondiabetic, exhibit hypoglycemia in response to the infusion of pancreatic vein blood from donor animals treated with sulfonylureas but not to the infusion of mesenteric or femoral vein blood from the same animals. Sulfonylureas cause degranulation of the β cells, a phenomenon associated with increased rate of secretion of insulin. Clinical studies demonstrate that the sulfonylureas are ineffective in completely pancreatectomized patients and in juvenile-onset diabetic subjects. On the other hand, they are effective in maturity-onset diabetic patients in whom the pancreas retains the capacity to secrete insulin.