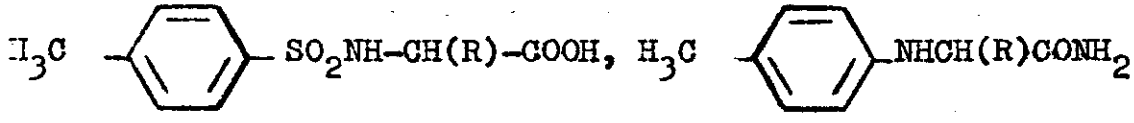
INTRODUCTION

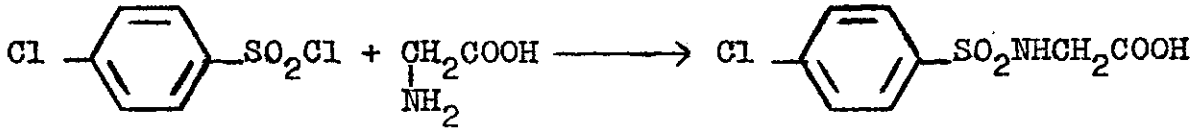
BIOLOGICALLY ACTIVE AROMATIC-SULPHONYL AMINO ACID DERIVATIVES

Several arylsulphonyl amino acids, amides, hydrazides and their derivatives were prepared and tested for their blood-sugar lowering activity in rabbits. (1)

Recently; Budenisky et al., (2) reported that certain alkyl p-toluenesulphonamides carboxylic acids possessed up to 60 percent of the hypoglycemic activity of tolbutamids. Several analogoues of such compounds have subsequently been synthesized and tested for their blood sugar lowering property (3). With a view to studying the effect of introducing a methylene residue in the urea moeity of hypoglycemic sulphonylureas, Dhar and Co-workers (4) have synthesized and tested some N-tosylamino acid amides. Later on, several aryl sulpho amino acids, amides and hydrazides were reported with the evolution of the hypoglycemic activity.



Initially, some phenylsulphonyl glycines and their N-derivatives with different substituents in the phenyl ring prepared and tested. Aryl-sulphonylglycine was prepared by slow addition of arylsulphonylchlorides available or obtained by chlorosulphonation, to a solution of glycine in 2-N sodium hydroxide and subsequent acidification gave the desired product.

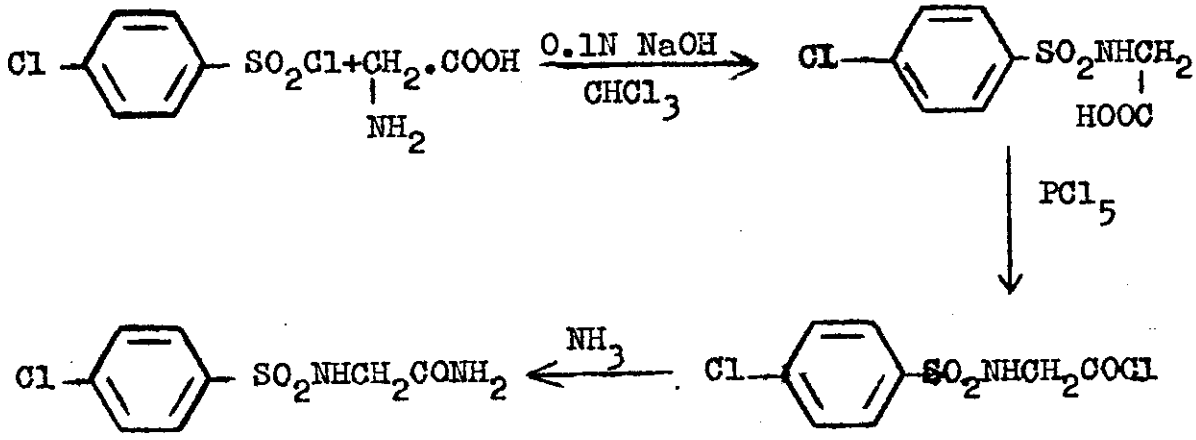


The last derivatives were then condensed with several amines usually selected in the synthesis of hypoglycemic sulphonylureas. Synthesis of such derivatives by condensing the acid chlorides with the amines or the N-alkylsulphonamides with the chloroacetylamino derivatives was not smooth and the yield were poor. However, a facile condensation with the appropriate amino could be achieved through an intermediate mixed acetic anhydride prepared according to Wailand and Shiping (5) by treatment of the glycine compound with acetylchloride in the presence of pyridine.

The p-chlorophenylsulphonylglycine hydrazides, and the semicarbazide derivatives and the p-tolyl-(n-butyl)

derivative were prepared and tested and the semicarbazides were found to possess appreciable antidiabetic activity.

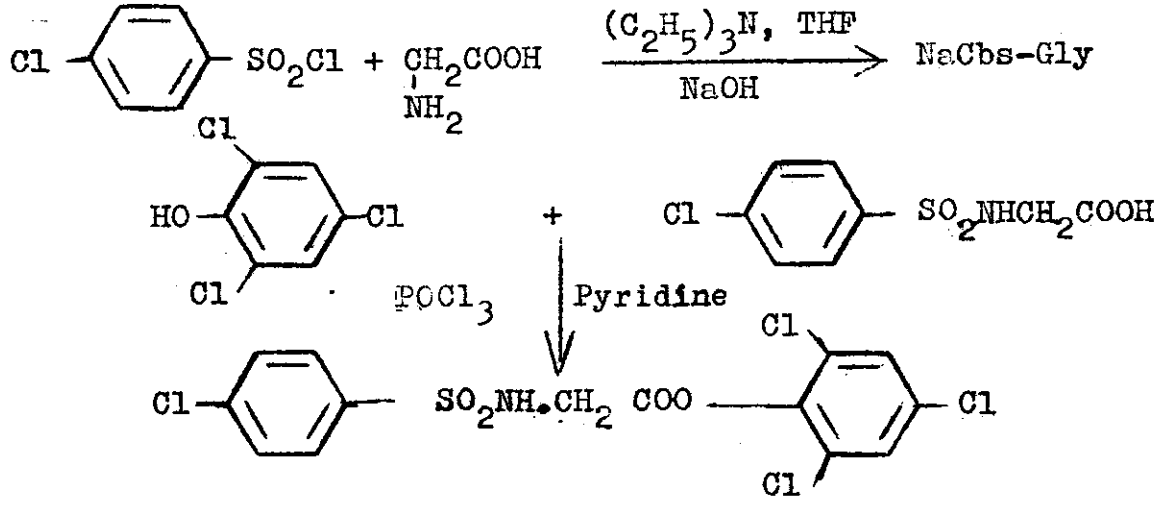
Jensen et al. (6) prepared p-chlorobenzene sulphonyl derivatives of some amino acids: glycine, α-alanine, β-alanine and phenylglycine and transformed them into the corresponding acid chlorides. From these some amides were prepared.

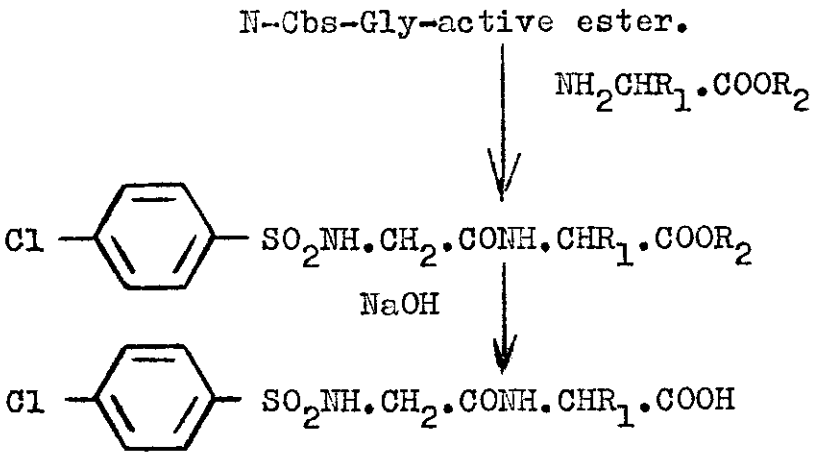


The author prepared the amino acid derivatives using p-chloro benzene sulphonlychloride in chloroform and the appropriate amino acid in 0.1 mole. NaOH. N-(p-Chlorobenzenesulphonyl)-dipeptides were obtained by the aminolysis of 2,4,6-trichloro phenylester of N-(p-chlorobenzene sulphonly) amino acids with alkyl esters of amino acids. The alkyl (3-tosyl amino acyl)- urees were synthesized by condensation of N-tosylamino acids or their acid chlorides with N-alkyl urees.

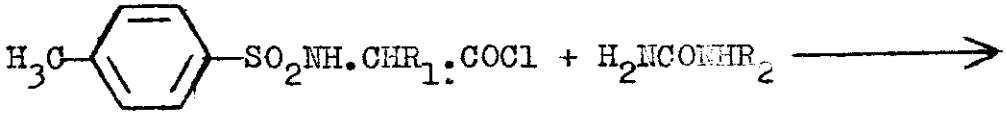
Discover of the hypoglycemic activity of some sulphonyl derivatives of amino acids and dipeptides was already known since L-leucine has been shown to have a weak hypoglycemic activity (7), therefore a series of its dipeptides was prepared.

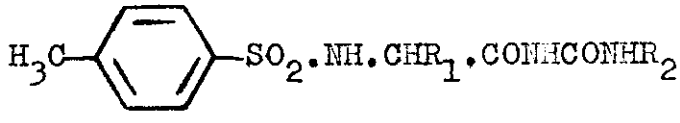
Condensation of p-chlorobenzenesulphonyl chloride with the corresponding amino acids in tetrahydrofuran (THF) in the presence of triethylamine or in aqueous NaOH gave the desired products. The active trichlorophenyl ester of the sulphonyl amino acid derivatives was obtained from N-Cbs-amino acids and 2,4,6-trichlorophenol by the method of mixed anhydrides using $POCl_3$. The product was treated with methyl or ethyl esters of glycine or L-leucine to give the corresponding alkyl esters of N-Cbs-dipeptides. After hydrolysis of the dipeptide with NaOH in acetone, the free N-Cbs-dipeptides were obtained in high yield.





1-Alkyl-3(Tosylamino acyl)-urees were prepared, since it was anticipated that the combination of active anti-diabetic moeities with amino acid systems might favorably potentiate the hypoglycemic activity of the compounds. These derivatives were synthesized by condensation of N-tosylamino acids or their acid chlorides with N-alkyl ureas. The reaction of N-tosyl amino acids with N-alkyl ureas was carried out using $POCl_3$ as a condensing agents.





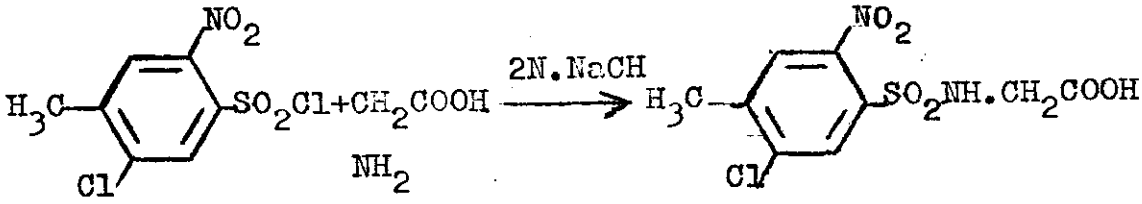
R_1 = H or $CH_2CH(CH_3)_2$; R_2=CH_3, C_2H_5, C_3H_7, n-C_4H_9

N-Cbs-amino acids independently of the carbon chain length of amino acid did not show hypoglycemic activity. Examination of the N-Cbs-dipeptides and 1-alkyl-3-(Tos-amino acyl) ureas showed that only 1-n-butyl-3(Tos-aminopropionyl)-ureas exerted a week hypoglycemic activity. The authors, showed that modification of the tolbutamide molecule by introduction of an additional amino acid rest leads to the loss of hypoglycemic activity.

N-Butyl-p-butoxy-phenylsulphonylglycine and p-Cl-$C_6H_4SO_2$- Gly as well as fifteen other amino acid derivatives were synthsized and found to be 73, 72% as active as tolbutamide. The compounds possessed a high hypoglycemic activities (8).

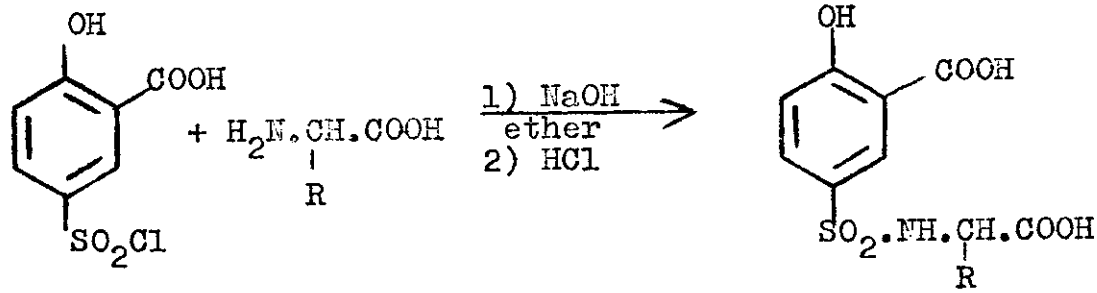
Nicotinunic acid, isonicotinunic acid and picolinuric acids and some new N-butyl- -amino acids acylated by pyridine carboxylic acids were prepared and tested for their hypoglycemic activity (9). All substances were prepared from pyridine carboxylic acid chlorides with amino acid ethyl esters followed by hydrolysis of the resulting ester. All substances prepared showed hypoglycemic activity in rats, but they were less effective than N-p-toluenesulphonyl-N^2-butylurea. Another derivatives such as 1-(p-toluensulphonyl) and 1-(p-chloro-benzenesulphonyl-3-alkylhydantoins have been reported (10).

Treating of glycine in 2N-sodium hydroxide with 2-nitro-4-methyl-5-chlorobenzene sulphonyl chloride followed by acidification with 5N-HCl gave the desired N(2-nitro-4-methyl-5-chlorophenylsulphonyl) glycine. The last was converted to the corresponding N(2-amino-4-methyl-5-chlorophenylsulphonyl) glycine by reduction.



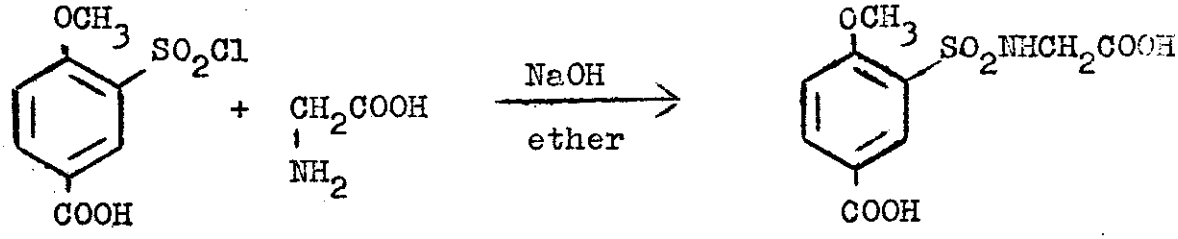
Some other derivatives of the various esters or amides were reported and they showed a low hypoglycemic activity (11).

Several N(3-carboxy-4-hydroxyphenylsulphonyl) amino acids were readily obtained by direct reaction of 5-chloro sulphonyl salicylic acid with appropriate amino acid in NaOH-ether medium. Coupling reaction with glycine, alanine, valine, leucine, serine, phenyl alanine, and tyrosine needed 1:1, 1 mole of the amino acid and 5-chlorosulphonyl salicylic acid respectively (12).



Some 3- carbomethoxy, 4-acetoxy and the hydrazide derivative of the synthesized derivativeswere prepared for studies of the structure activity relationships. These amino acid derivatives are expected to possess some hypoglycemic activities however all were biologically inactive against some microorganism.

Another group of compounds such as N(2-methoxy-5-carboxyphenylsulphonyl) Gly, B-ala and L-tyrosine containing anisic acid incorporated with sulphonyl amino acid residue, were also prepared in ether-NaOH medium.



Some anisylsulphonyl amino acid derivatives is expected to possess hypoglycemic activities (13).

Several 2-amino-5-carboxy-benzene sulphonylamino acids were readily prepared by direct reaction of 2-amino-5-carboxybenzene sulphonyl chloride with the appropriate amino acid in sodium hydroxide-water mixture. Coupling reaction with glycine, L-valine, DL-serine and L-alanine