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Notes

Synthesis and Oral Hypoglycemic Activity of *N*-(*p*-Deuteriomethylbenzenesulfonyl)-*N'*-*n*-butylurea, Deuterium-Substituted Tolbutamide[1]

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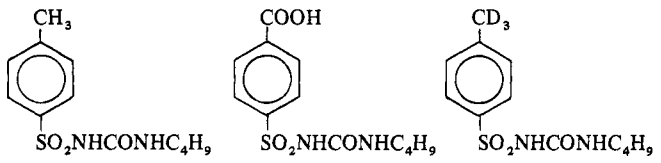
The primary metabolic pathway for the oral hypoglycemic agent, *N*-(*p*-methylbenzenesulfonyl)-*N'*-*n*-butylurea (I) (tolbutamide) is oxidation of the aromatic Me group to the inactive carboxylic acid (II) which is excreted.[1]



If the rate-determining step in the metabolic deactivation of the compound involved breaking of a C-H bond, then the rate of deactivation of *N*-(*p*-deuteriomethylbenzenesulfonyl)-*N'*-*n*-butylurea (III) would be slower due to the higher energy necessary to break the C-D bond of III.[2,3] This would result in a substantially increased duration of activity, which might enable the dosage necessary for a particular pharmacological result to be reduced appreciably with a corresponding decrease in the undesirable side effects of the drug.

III was prepared in a reaction sequence starting with toluene-d_8, which is commercially available in 99% isotopic purity.† The toluene-d_8 was sulfonated with HSO_3Cl and the resulting acid chloride was converted to the amide with concd NH_4OH, which was then converted to the disubstituted urea (III) with *n*-butyl isocyanate.[4] An nmr comparison of the residual protons of the *p*-deuteriomethylbenzenesulfonyl chloride with that of the 99 atom % toluene showed that the ring was only about 90% deuterated, indicating that some exchange had occurred during sulfonation. The Me group was still 99 atom % D in both the *p*-deuteriomethylbenzenesulfonyl chloride and in the final product, III. The D compound III melted at 126-127° as did the proteo compound and a mixture of the two.

The hypoglycemic activity of I and III was compared in male rats and found to be equiv (equal on a mole to mole basis). The deuterated material was not different in total activity or onset or duration of activity.

From these results, it can be concluded that the rate-determining step in the metabolic deactivation of I by its conversion to II does not involve the breaking of a C-H bond in the Me group ultimately oxidized to CO_2H.

Experimental Section

***p*-Deuteriomethylbenzenesulfonyl Chloride.** To a soln of 10 g (0.1 mole) of toluene-d_8 (99 atom % D)† was added 20 ml (0.33 mole) of HSO_3Cl dropwise with stirring. The temp rose 20°. Stirring was contd for 0.5 hr and the mixt was poured into ice. The org layer was sepd and the solvent was evapd. The solid was recrystd twice from hexane; yield 10.5 g (55%), mp 66-68° (lit.[5] proteo-*p*-toluenesulfonyl chloride, 69°). The nmr spectrum of the residual protons in this material in $DCCl_3$ compared to an equimolar soln of toluene-d_8 (99 atom % D), showed the same CH_3 absorption, but showed about 8 times the arom H absorption.

***p*-Deuteriomethylbenzenesulfonamide.** *p*-Deuteriomethylbenzenesulfonyl chloride (9.8 g, 0.05 mole), was added to 100 ml of concd NH_4OH and the mixt was stirred overnight at room temp. The solid was collected on a filter; wt 3.2 g, mp 127-132°. The mother liquor was acidified with concd HCl. The solid was collected, washed twice

†Diaprep, Inc., Atlanta, Georgia 30301.

(H_2O), and recrystd from EtOH; yield 5.9 g (69%), mp 137–138°, lit.[5] for proteo-*p*-toluenesulfonamide, mp 137°.

***N*-(*p*-Deuteriomethylbenzenesulfonyl)-*N'*-*n*-butylurea (Deuteriomethyltolbutamide).** A mixt of 5.7 g (0.033 mole) of *p*-deuteriomethylbenzenesulfonamide, 9 g of dry K_2CO_3, and 45 ml of acetone (dried over $CaCl_2$) was heated to boiling under reflux with stirring. *n*-Butyl isocyanate (3.3 g, 0.033 mole) was added dropwise during 10 min and the mixt was boiled under reflux for 6 hr. The acetone was evapd and the residue was dissolved in 100 ml of H_2O. The soln was acidified with 5% HCl and the cryst solid was collected on a filter. The solid was dissolved in 75 ml of 5% NH_4OH, the soln was treated with charcoal and filtered, and the clear colorless soln was acidified by adding 5% HCl dropwise with stirring. The solid was collected and recrystd from 50% EtOH; yield, 7.2 g (78%), mp 126–127°, lit.[4] for proteotolbutamide, mp 125–127°. The nmr spectrum of this material in 5% K_2CO_3 in D_2O compared to an equimolar soln of toluene-d_8 (99 atom % D) showed the same arom Me absorption and about 8 times the arom H absorption.

Hypoglycemic Activity of Deuteriomethyltolbutamide. The hypoglycemic activity was measured by oral administration of graded doses of deuteriotolbutamide to a set of 5 male rats that had been fasted for 18 hr prior to dosing. The animals received a priming dose of 125 mg of glucose, sc, in 1 ml of saline. Blood sugar concns were measured at intervals for 4 hr thereafter. The values were compared to the concns in an equiv set of animals receiving no test compound. The results obtd from the D-substituted material were the same as those for the material with no D, in total activity and in onset and duration of activity.

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Polymers Containing Phenethylamines

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The attachment of compounds having pharmacological activity to polymers has been of interest lately as a method for increasing their duration of action.[1-11] In the present work the effect of the attachment of various phenethylamines to polymers either by an amide or carbamate linkage to both synthetic and natural polymers was investigated. These linkages are expected to be hydrolyzable in the body, thus setting free the phenethylamines. The phenthylamines investigated were phenylethylamine, *dl*-amphetamine, *l*-ephedrine, and tyramine. Polymethacrylic acid and starch were used as polymer backbones for the attachment of the phenethylamines.

To obtain the polymers based on methacrylic acid, suitable monomers, *viz.* the *N*-methacryloyl derivatives of the phenethylamines were prepared and polymerized. The *N*-methacryloylphenethylamines were obtained by reaction of methacryloyl chloride with the phenethylamines. They

$$-CH_2CH_2NH_2 + CH_2{=}C(CH_3)COCl \longrightarrow -CH_2CH_2NHCOC(CH_3){=}CH_2$$

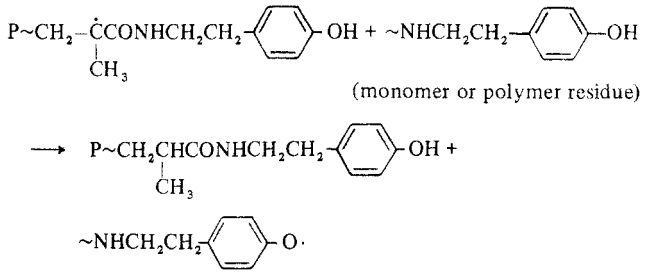
were not subject to rapid polymerization under usual laboratory conditions, and were polymerized radically in bulk (Table I).

Table I. Polymerization of *N*-Methacryloylphenethylamines

Monomer[a]	Yield, %	Polymer[c] Recryst solvent	Polymer[c] Mp range, °C
I	92	$CHCl_3$-Et_2O	127–150
II	80	$CHCl_3$-Et_2O DMA-H_2O	142–156
III	10	$CHCl_3$-Et_2O	143–162
IV[b]	98	*d*	245–300

[a] For definition of monomers see Experimental Section. [b] Polymerized at 130°, for 3 days. [c] *Anal:* N. [d] Slightly sol in DMA; insol in ordinary org solvents.

N-Methacryloyltyramine behaved differently from the others, and insoluble cross-linked polymers were formed which set as gels. It seems that transfer reactions to the phenolic group may have been the cause for the cross-linking. The phenolic radical formed can give more stable



products, for example, *via* oxidative coupling reactions[12,13] both inter- and intramolecular, forming new C-C, C-O, and O-O bonds.

Since biological activity is expected to be greatly affected by physical properties such as solubility, partition coefficient, and permeability to physiological membranes, it was of interest to prepare copolymers of the *N*-methacryloylphenethylamines with methacrylic acid, vinyl acetate, and vinylpyrrolidone (Table II).

The phenethylamine derivatives of starch (Table III) were prepared by treating the phenethylamines with the chloroformate starch derivative.

$$\text{Starch-OH} + \text{ClCOCl} \longrightarrow$$

$$\text{Starch-OCOCl} \xrightarrow{NH_2CH_2CH_2C_6H_5} \text{Starch-OCONHCH}_2\text{CH}_2\text{C}_6\text{H}_5$$

The chloroformate ester of the starch is quite stable and can be stored. It can be used as a starting material for the formation of various derivatives of starch such as esters and amides.

To find out the effect of the amount of phosgene on the reaction, an experiment was carried in which 0.33 equiv of $COCl_2$ per OH was added. The product however on subsequent reaction with amine gave a degree of substitution of about 0.33 of that obtained in the previous reactions. On working under more drastic conditions, *viz.* higher temp and longer reaction time, it was possible to increase considerably the degree of substitution of the amine attached to the starch.

There is the possibility of cross-linking reactions in which the chloroformate groups on one chain may react with free OH groups on another forming a carbonate linkage, but the fact that the starch derivatives remained almost completely soluble in hot DMSO shows that the degree of cross-linking is very small.

Preliminary Pharmacological Evaluation. Preliminary