(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

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

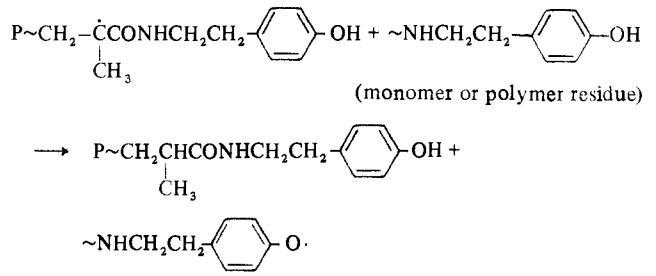
were not subject to rapid polymerization under usual laboratory conditions, and were polymerized radically in bulk (Table I).

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

Table II. Copolymerization of *N*-Methacryloylphenethylamines and Vinyl Monomers

Vinyl monomer	Phenethylamine monomer[a]	Yield, %	Recryst solvent	Mp range, °C	N, %	Composition: Phenethylamine monomer, %	Composition: Vinyl monomer, %
Methacrylic acid	I	75	MeOH-H_2O MeOH-H_2O	180–206	5.1	68.8	31.2 (29.1)[b]
	II	72	MeOH-H_2O	224–254	3.4	49.8	50.2 (51.3)
	III	50	MeOH	214–225	3.1	51.6	48.4 (50.1)
	IV	71	*c*	Over 300	6.8	100	0 (0)
Vinyl acetate[d]	I	35	$CHCl_3$-Et_2O	113–125	6.4	86.5	13.5
	II	43	$CHCl_3$-Et_2O	116–125	5.2	73.9	26.1
Vinylpyrrolidone[e]	I	71	$CHCl_3$-Et_2O	125–136	8.1	91.4	8.6
	II	78	$CHCl_3$-Et_2O	154–164	8.8	72.4	27.6

[a]For definition of monomers see Experimental Section. [b]Copolymer comp was calc from %N. The values given in parentheses were det by titration. [c]Insoluble polymer contains only *N*-methacryloyltyramine. [d]No copolymers were obtd from monomers III and IV. [e]With III insignificant amts of copolymer were formed, mp 142–155°.

Table III. Phenethylamine Derivatives of Starch[a]

Amine	N in product, %	Degree of substitution of amine per glucose	Number of glucose molecules per amine
Phenethylamine	0.52	0.06	16
Phenethylamine	3.01	0.47	2
DL-Amphetamine	0.50	0.07	15
DL-Amphetamine	1.73	0.26	4
DL-Amphetamine	2.26	0.36	3
L-Ephedrine	0.50	0.06	16
Tyramine	0.55	0.07	15

[a]Starch was converted to the chlorocarbonate derivative by reaction with $COCl_2$ and then treated with the phenethylamines.

tests were carried out on the monomeric *N*-methacryloylphenethylamines, their polymers and copolymers, as well as on the phenethylamine starch derivatives. General behavioral changes were observed on administration of the compounds to mice, and the effect of blood pressure was tested on cats. The results (Tables IV, V) indicate that in general there is basis to show that the duration of activity of the polymers was greater than that of the monomers. The toxicity of the compounds is much smaller than that of the parent drugs as seen from the LD_{50} values (compare LD_{50} of amphetamine (mice iv) = 25 mg/kg; MLD (rat ip = 4 mg/kg). Further the mode of action of the polymeric compounds was sometimes in contrast to that of the parent phenethylamine. Thus the copolymer of *N*-methacryloylamphetamine with vinyl acetate showed depressant activity (Table IV) in contrast to amphetamine, although it also increased the blood pressure.

In the case of the phenethylamine derivatives, it was found (Table IV) that with *N*-methacryloylphenethylamine monomer onset of action was almost immediate (2 min after injection), symptoms continuing longer than 6 hr. The deaths observed at the higher dose level, occurred 20 min after injection, and this is in contrast to the homopolymer where the deaths occurred only after 2 days, and the copolymer with methacrylic acid where they occurred 1–3 days after injection.

N-Methacryloylephedrine was active for about 4 hr as compared to its copolymer with methacrylic acid which showed activity up to 48 hr.

As regards the phenethylamines attached to starch, it can be seen that the duration of action was more than that of phenethylamine itself. Thus in the case of phenethylamine attached to starch (Table V) (25.9% in product), sedation was observed to continue from 5 to 24 hr and deaths occurred between 2 and 6 days.

It is interesting that all the phenethylamine derivatives investigated had a similar type of activity. All showed hypopnea. On the other hand with the amphetamine derivatives, the *N*-methacryloyl monomer did not show any special effect, while the copolymer with methacrylic acid showed hyperpnea and the copolymers with vinyl pyrrolidone and vinyl acetate showed hypopnea.

The monomers and polymers showed only small variations on blood pressure in tests conducted on cats.

In the case of the amphetamine derivatives all the compounds showed an increase in blood pressure, especially the copolymer with vinyl acetate which caused a large increase (40% rise in blood pressure in 3.5 hr).

In general no obvious effects were observed on the blood pressure with added reference drugs (epinephrine, norepinephrine, histamine, and ACh).

Since one possible mode of action of the polymeric compounds is their prior hydrolysis in the body (both chemical and enzymatic) to the parent phenethylamine, it was decided to investigate the acid hydrolysis of the new phenethylamine monomers and polymers. HCl (0.1 *N*) was used and the hydrolysis was conducted at 37°. It was found (Table VI) that the per cent hydrolysis increased with time, and the polymers suffered slower hydrolysis than the monomers.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncor. Nmr spectra were taken on a Varian T-60 instrument, and ir on a 257 Perkin-Elmer instrument. Where analytical results are indicated only by the symbols of the elements, the observed values differed from the calculated values by not more than ±0.4%.

N-Methacryloyl-β-phenethylamine (I). Methacryloyl chloride (1.05 g, 0.01 mole) in Et_2O (10 ml) was added dropwise with stirring during 30 min to a cooled soln of phenethylamine (1.22 g, 0.01 mole) and Et_3N (1.01 g, 0.01 mole) in Et_2O (100 ml). The reaction mixt was stirred for 1 hr and filtered from insol $Et_3N \cdot HCl$, and the Et_2O was dist *in vacuo*. The residue was recrystd several times from Et_2O-petr ether (ice-salt mixt: yield 1.8 g (93%); mp 32.5°. Similar yields were obtd on carrying out the reaction in $CHCl_3$. The monomer is soluble in H_2O, EtOH, DMA, and CCl_4: ir 3300 (NH), 1615 (C=C), 1660 (C=O), 700, 745 cm^{-1} (C_6H_5); nmr, δ 1.9 (s, 3, C-CH_3), 5.28, 5.64 (d, 2, C=CH_2); 7.23 (s, 5, C_6H_5). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

N-Methacryloyl-DL-amphetamine (II) was prepd as above in 85% yield: mp after recrystn from EtOH-H_2O, 61.5°; ir 3290 (NH) 1615 (C=C) 1650 (C=O) 700, 745 cm^{-1} (C_6H_5); nmr, δ 1.15 (d, 3, CCH_3); 1.9 (s, 3, =C-CH_3) 5.29, 5.65 (d, 2, C=CH_2); 7.30 (s, 5, C_6H_5); 5.29 (s, 1, NH). *Anal.* ($C_{13}H_{17}NO$) C, H, N.

N-Methacryloyl-L-ephedrine (III) was prepd as above in 87% yield: mp after recrystn from EtOAc-petr ether, 72°; ir 3250 (OH), 1645 (C=O), 700, 745 cm^{-1} (C_6H_5); nmr, δ 1.25 (d, 3, CCH_3), 1.72

Table IV. Mono- and Poly(methacryloylphenethylamines)

Compound[b]	% phenethylamine in product	General behavioral changes[a] Deaths at mg/kg ip 500	1000	LD_{50}, mg/kg	Symptoms[c]
Monomer (I)		0	2	>1000	Ataxia 2 min after injection, hypopnea, gasping, loss of righting reflex, which continued longer than 6 hr; deaths occur 20 min after injection
Homopolymer (I)		0	3	>1000	Hypopnea, stress, highest dose prostration; deaths occur after 2 days
Copolymer (I + MA)	43.7	0	6	800	Sedative, ataxia; deaths occur 1-3 days after injection
Copolymer (I + VA)	54.9	0	0	>1000	Depressant 5 to 10 min, hypopnea hypoactivity; recovery at about 1 hr
Copolymer (I + VP)	58.2	0	0	>1000	Hypopnea, depressant at high dose–appears shortly after administration; lasts for 5 hr
Monomer (II)		0	0	>1000	No special symptoms
Homopolymer (II)		1	7	900	Hyperpnea–starting at 10 min; no special symptoms after 3 hr
Copolymer (II + MA)	33.2	5	8	670	Symptoms appear at 2 hr–stimulation, hyperpnea, stretching; deaths up to 5 days
Copolymer (II + VA)	49.2	3	4	1000	Decreased activity, hypopnea, ptosis all within 30-60 min continuing 3 hr; at higher doses prostration; deaths extend over 5 days
Copolymer (II + VP)	48.2	0	0	>1000	A slight initial stimulation then sedation, hypopnea from 10 min; at little dose signs of stimulation at 2 hr
Monomer (III)		0	5	880	At higher doses hypopnea at 10 min; ataxia at 30 min, continuing hypopnea, lasts for 4 hr; deaths occur up to 3 days
Copolymer (III + MA)	36.4	0	8	700	Increase in activity–crying, salivation, stimulant over 20 hr then at 24 hr up to 48 hr; sedation set in with decreased activity, ataxia, ptosis slight tremoring of muscles
Monomer (IV)		1	7	900	Depressant hypopnea, 10 min to 4 hr; deaths up to 2 days; recovery of survivors occurs from about 4 hr

[a]Groups of 8 mice for each dose level were used. MA = methacrylic acid; VA = vinyl acetate; VP = vinylpyrrolidone. [b]For definition of monomers and polymers see Experimental Section. [c]Observed with the highest dose investigated.

Table V. Phenethylamines Attached to Starch

Amine	% phenethylamine in product	General behavioral changes Deaths at mg/kg ip 500	1000	LD_{50}, mg/kg	Symptoms[a]
Phenethylamine	4.5	0	0	>1000	No obvious ones; depressant at highest dose
Phenethylamine	25.9	0	2	>1000	Hypopnea decreased activity, defecation; death 48 hr to 6 days; sedation 5-24 hr; vasoconstriction noted
DL-Amphetamine	4.8	0	0	>1000	CNS stimulant, hyperpnea, salivation, lachrymation, at 5 hr symptoms wear off
DL-Amphetamine	16.7	0	4	1000	Hyperpnea at 5 min, stimulant; hyperactivity, "Straub" tail, symptoms last from 4 to 6 hr depending on dose; deaths at 2.5 hr
DL-Amphetamine	21.8	2	4	1000	Mainly decreased activity, onset in 0.5 hr, continuing 30 hr; deaths 3 days
L-Ephedrine	5.9	0	0	>1000	Hypopnea, stretching, lachrymation, sedation at 10 min, recovery 3 hr
Tyramine	5.5	0	0	>1000	Sedative, onset 0.5-2 hr, present at 24 hr

[a]Observed with the highest dose investigated.

(s, 3, $=CCH_3$), 2.80 (s, 3, NCH_3), 4.35 (s, 1, OH), 4.72, 5.06 (d, 2, CCH_2), 7.37 (s, 5, C_6H_5). *Anal.* ($C_{14}H_{19}NO_2$) C, H, N.

N-Methacryloyltyramine (IV). Tyramine (2 g, 0.0146 mole) was dissolved in pyridine (100 ml), and methacryloyl chloride (1.528 g, 0.0146 mole) in dry Et_2O (2 ml) was added dropwise with stirring at room temp. The reaction mixt became dark red and was stirred for 8 hr. Et_2O (4-5 vol) was added, and the ppt of pyridine hydrochloride was separated. The filtrate was evapd to dryness *in vacuo*, H_2O was added, and the *N*-methacryloyltyramine was collected and recrystd from H_2O: yield 1.6 g (55%); mp 119°. It is soluble in DMA and slowly in propylene glycol: ir 3340 (NH), 1650 (C=O), 825 cm^{-1} (p-C_6H_4); nmr, δ 3.80 (s, 1, OH), 5.21,

Table VI. Hydrolysis of Monomeric and Polymeric Phenethylamine Derivatives[a]

Compound[b]	Time of reaction, hr	Hydrolysis, %
Monomer I	72	45.3
Homopolymer I	72	37.8
Monomer II	72	74.0
Homopolymer II	72	36.0
Phenethylamine–starch (%N 3.01)	72	46.2
DL-Amphetamine–starch (%N 2.26)	72	22.8
Monomer I	3	1.9
	6	5.7
	24	19.0
	48	28.3
	72	45.3
Homopolymer I	3	0
	6	3.8
	24	9.4
	48	22.6
	72	37.8

[a]Hydrolysis was carried out using 10 mg of compound which was suspended in 1 ml of 0.1 *N* HCl and heated at 37°. Extent of hydrolysis was followed by titration with 0.1 *N* NaOH using phenolphthalein as indicator. [b]For definition of monomers and polymers see Experimental Section.

5.46 (d, 2, C=CH_2), 6.80 (q, 4-C_6H_4). *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

Polymerizations and Copolymerizations. The polymerizations were carried out in bulk without solvent (except where indicated) under Ar at 90° during 4 days using 3–4% azobis(isobutyronitrile) as catalyst. The results are summarized in Tables I and II. All polymers were doubly recrystd before biological tests, so that they did not contain any monomers residues as seen from ir and nmr spectra. The fact that the monomers were soluble in Et_2O made the purification easy. The polymers were insoluble in H_2O.

Phenethylamine Derivative of Starch. Soluble starch (Analar, BDH) (0.575 g) cont 15% H_2O and 0.003 mole of anhydroglucose units was suspended in H_2O (1 ml) and pyridine (1 ml) and heated until it dissolved. To clear soln pyridine (20 ml) was added. The mixt was mechanically stirred while the pyridine was slowly distd off until the boiling point of the distillate reached 115°, that of dry pyridine. The resulting suspension of dry starch in pyridine (~10 ml) was cooled in ice–salt mixt and $COCl_2$ (0.01 mole) in a 12.5% soln in PhMe was added. The reaction mixt was stirred for 12 hr at room temp and then cooled to 5°, and phenethylamine (2.42 g, 0.02 mole) was slowly added. The reaction mixt was stirred for 30 min in the cold and then for 20 hr at room temp. EtOH was added, and the ppt was washed with EtOH or H_2O until the wash liquors were free from Cl^-: yield, 0.3 g; %N = 0.5, equiv to 4.5% of phenethylamine attached to starch. The product contd chlorocarbonate groups (ir 1810 cm^{-1}) which were decompd by boiling the product for 30 min in H_2O. No ethoxy formate esters of starch were formed (ir).

The reactions with DL-amphetamine, L-ephedrine, and tyramine were carried out similarly.

To obtain a higher degree of substitution of the phenethylamines on the starch, the above procedure was modified as follows. After addn of the phenethylamine to the chlorocarbonate derivative of the starch in pyridine, the reaction mixt was stirred for 4 hr at room temp and then for 15 hr in an oil bath at 60°: yield, 0.65 g, %N = 3.0, equiv to 25.9% phenethylamine attached to starch.

Preliminary Pharmacological Evaluation. For gross behavioral changes and dose-range finding experiments all compds were administered as neutral solns in dose volumes of 10 ml/kg ip to male Swiss Albino mice (19–21 g) as suspensions in 1% gum tragacanth. Eight mice were in each group, and there were 3 groups each having a different dose, the doses being 500 and 1000 mg/kg. Mice were observed for periods up to 6 hr, then returned to their cages, and observed further for 1 week. Standard laboratory diet and H_2O were allowed *ad lib* and they were housed with other laboratory rodents in the same conditions. Comparisons were always made with controls.

Effects on blood pressure were studied. For each compd 2 cats of both sexes weighing 2–3.5 kg were anesthetized with 40 mg/kg of pentobarbital ip and prepd for blood pressure recording using the Grass Model 8 polygraph. Extraneous reference substances, epinephrine, norepinephrine, histamine, and ACh were used to determine effects of the compds on physiological substances. The compds, where possible, were given as 10 mg/kg iv single doses, or when absolutely insoluble, as 100 mg/kg ip suspension in 1% gum tragacanth. Observations extended to 3.5 hr while reference physiological substances were given every hour.

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Potential Psychotomimetics. New Bromoalkoxyamphetamines

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The publications by Shulgin[1] and by Barfknecht[2] of the preparation and preliminary pharmacological evaluation of several bromoalkoxyamphetamines prompted us to publish some data on 2 additional compounds belonging to this series.[3] As pointed out by Barfknecht,[2] the Br atom is comparable in size but not in electronic character to the Me group. The MeO group also approaches the size of the Br atom, but its electronic configuration is quite similar, so much so that Hückel's LCAO-MO approximation shows no clear differences between the molecular parameters of the trialkoxy- and bromodialkoxyamphetamines.† However, the relatively high psychotomimetic potencies of 2,4,5-trialkoxyamphetamines increase more than tenfold when the para substituent is replaced by an alkyl group[4] or by a Br atom.[1] Attempts to relate psychotomimetic potency to electronic configurations and to hypothetical preferred conformations[5-7] are thus severely limited by other factors such as, probably, metabolic lability of different substituents at key locations in the molecule, notably ortho and para to the amine side chain.

Chemistry. The recently reported[2] 2-bromo-4,5-dimethoxyamphetamine and the new 2-bromo-4,5-methylenedioxy- and 5-bromo-2,4-dimethoxyamphetamines were prepared, as the hydrobromides, by bromination of 3,4-dimethoxy-,

†A. Suárez, E. Sanhueza, and B. K. Cassels, unpublished results.