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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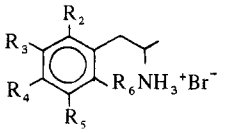
The publications by Shulgin[1] and by Barfknecht[2] of the preparation and preliminary pharmacological evaluation of several bromoalkoxyamphetamines prompted us to publish some data on 2 additional compounds belonging to this series.[3] As pointed out by Barfknecht,[2] the Br atom is comparable in size 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-,

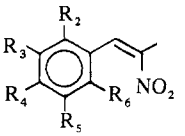
†A. Suárez, E. Sanhueza, and B. K. Cassels, unpublished results.

Table I. Bromoalkoxyamphetamine Hydrobromides

Compd	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula[a]
								
1	Br	H	OMe	OMe	H	210	8	$C_{11}H_{17}Br_2NO_2$
2	Br	H	OCH_2O		H	221-222	61	$C_{10}H_{13}Br_2NO_2$
3	OMe	H	OMe	Br	H	204.5-205.5	67	$C_{11}H_{17}Br_2NO_2$

[a]All compds were analyzed for C, H, N, and Br.

Table II. 1-Bromoalkoxyphenyl-2-nitropropenes.

Compd	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula[a]
								
4	Br	H	OMe	OMe	H	105-106	75	$C_{11}H_{12}BrNO_4$
5	Br	H	OCH_2O		H	157.5-158.5	73	$C_{10}H_8BrNO_4$
6	OMe	H	OMe	Br	H	123.5-124	94	$C_{11}H_{12}BrNO_4$

[a]All compds were analyzed for C, H, and Br.

Table III. Biological Results

Compd	ED, mmoles/kg	Activity, MMU[a]	Action
2	0.015	<1.2	Amphetamine-like
3	0.0040	4.4	MDA-like

[a]Molar mescaline units: effective dose of mescaline (mmoles/kg)/effective dose of compound (mmoles/kg). Effective dose of mescaline = 0.0178 mmoles/kg.

3,4-methylenedioxy-, and 2,4-dimethoxyamphetamine, respectively (Table I). The structures of these products were confirmed by C, H, N, and Br analyses, and by nmr spectra showing in each case two distinct aromatic proton resonances with no appreciable splitting ($J \ll 1$ Hz).

For the sake of comparison of the nmr spectra, the corresponding substituted 1-phenyl-2-nitropropenes were synthesized by condensation of the appropriate benzaldehydes with $EtNO_2$ (Table II). The spectra of both groups of compounds were quite similar in the aromatic region.

The brominations of 3,4-methylenedioxy- and 2,4-dimethoxyamphetamine proceeded at widely different rates but with acceptable yields to furnish the new bromoalkoxyamphetamines here described. On the other hand, the bromination of 3,4-dimethoxyamphetamine yielded extremely small amounts of 2-bromo-4,5-dimethoxyamphetamine, precluding any pharmacological tests. Barfknecht and Nichols' route to this compound[2] is thus much more satisfactory in spite of the difficulties encountered by them in the LAH reduction of the corresponding brominated phenylnitropropene, apparently due to hydrogenolysis of the C-Br bond.

Biological Results. 2-Bromo-4,5-methylenedioxy- and 5-bromo-2,4-dimethoxyamphetamine were tested in humans as described by Shulgin and coworkers,[4] and their effects were compared with those produced by unsubstituted amphetamine and by 3,4-methylenedioxyamphetamine (MDA). The data on the new compounds are summarized in Table III.

Previous work has shown that the presence of metabolically stable groups or atoms para to the *i*-$PrNH_2$ side chain increases the potency of the amphetamines examined so far for psychotomimetic activity.[1,2,4,8] We feel that such groups or atoms ortho to the side chain may decrease the potency of the substances in which they occur by preventing this position from being occupied by OH, as suggested by the inactivity of 2-bromo-5-methoxy-,[2] 2-bromo-4,5-dimethoxy-,[2] and 2-bromo-4,5-methylenedioxyamphetamine as compared with their 2-MeO counterparts.[4] The effect of metabolically stable groups or atoms meta to the side chain is less clear.

Experimental Section‡

Bromoalkoxybenzaldehydes. 2-Bromo-4,5-dimethoxy-,[9] 2-bromo-4,5-methylenedioxy-,[9] and 5-bromo-2,4-dimethoxybenzaldehyde,[10] have been reported previously, and were prepd by bromination of the corresponding dialkoxybenzaldehydes in AcOH.

1-(Bromoalkoxyphenyl)-2-nitropropenes. The substituted benzaldehydes were refluxed with $EtNO_2$ and NH_4OAc in AcOH as described by Gairaud and Lappin.[11]

Dialkoxyamphetamines. These compds have been reported previously,[4] and were prepd by LAH reduction of the corresponding 1-dialkoxyphenyl-2-nitropropenes.

Bromoalkoxyamphetamine Hydrobromides. The dialkoxyamphetamines were dissolved in AcOH and treated at room temp with equimolecular amounts of Br_2 dissolved in AcOH. The crude hydrobromides were collected and recrystd from *i*-PrOH-Me_2CO.

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‡Melting points were taken on an Electrothermal apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtd for those elements were within ±0.4% of the theoretical values. Nmr spectra for all compds were obtd on 60 MHz instruments, and are consistent with the assigned structures.

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1*H*-Imidazo[1,2-*a*]imidazoles†

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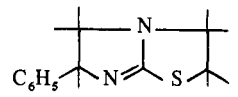
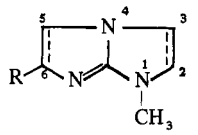
Tetramisole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]-thiazole) has been found to be a potent broad spectrum anthelminthic agent, effective for the treatment of helminthiases in domestic animals.[1] A logical extension of this development was the replacement of the thiazole S of tetramisole with a substituted N to give an aza analog which might be expected to demonstrate similar activity. Accordingly, the



tetramisole

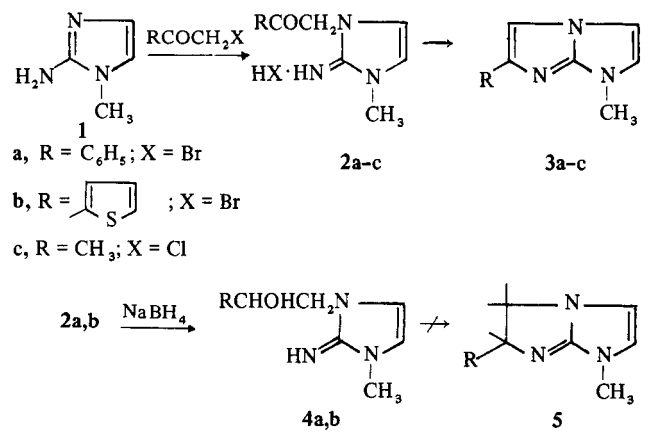


1-methyl-1*H*-imidazo[1,2-*a*]imidazole

synthesis of a series of 6-substituted 1-methyl-1*H*-imidazo-[1,2-*a*]imidazoles was undertaken, wherein the ring system was unsaturated, dihydrogenated, and tetrahydrogenated. The 6 position substituents chosen were methyl (unsaturated system only), Ph, and thienyl.

Chemistry. The imidazo[1,2-*a*]imidazole moiety was first reported by Pierron[2] in 1919, however, the vast majority of work in this area has been done by McKay and coworkers who prepared a series of 1-substituted 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazoles. McKay's method of synthesis[3] involved the reaction of 1-(2-hydroxyethyl)imidazolidin-2-thione with a primary amine, giving an amino-substituted 2-aminoimidazoline which was then treated with $SOCl_2$ and base to yield a bicyclic product. This method was not particularly applicable to our needs. We felt that we could more easily prepare the target compounds by alkylation of 2-amino-1-methylimidazole (**1**) or 2-amino-1-methylimidazoline (**6**) with an α-halo ketone. Thus, reaction of **1** (Scheme I) with 2-bromoacetophenone yielded 2-imino-3-methyl-1-phenacyl-4-imidazoline hydrobromide (**2a**). Similarly, reaction of **1** with 2-(bromoacetyl)thiophene[4] and chloro-2-propanone gave **2b** and **2c**, respectively. **2a** and **2c** were readily cyclized to the 6-substituted 1-methyl-1*H*-imidazo-[1,2-*a*]imidazoles (**3a,c**) by refluxing in dil acid. **2b** was more resistant to cyclization, requiring polyphosphoric acid.

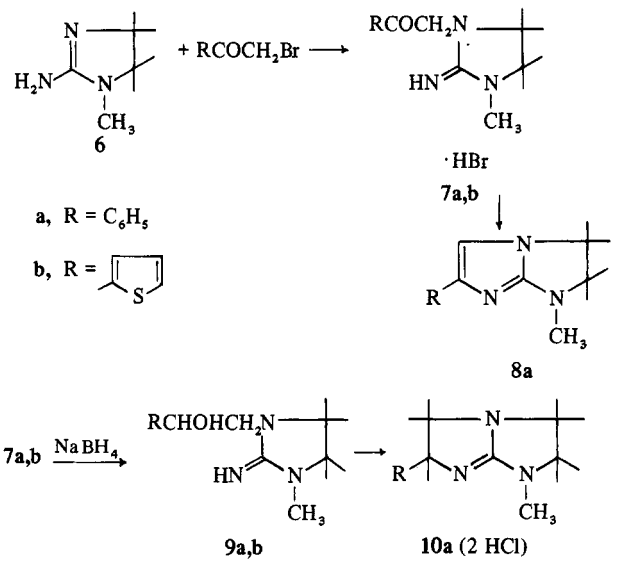
Scheme I



Attempts were made to prepare 6-substituted 5,6-dihydro-1*H*-imidazo[1,2-*a*]imidazoles (**5**). Reduction of **2a** and **b** with $NaBH_4$ gave the expected β-substituted hydroxyethyl derivatives (**4a, b**), however, in our hands these could not be converted to the bicyclic products.

Alkylations of **6** (Scheme II) were accomplished by methods similar to those described for **1**, giving **7a** and **b**. **7a** was readily converted to **8a** in concd acid, however, the thiophene derivative (**7b**) resisted cyclization. Reduction of **7a** and **b** with $NaBH_4$ gave **9a** and **b**, respectively. Treatment of **9a** with $SOCl_2$ gave the tetramisole analog, 1-methyl-6-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole (**10a**), however, **9b** could not be cyclized. **10a**, which was isolated as its dihydrochloride salt, showed a double melting point and investigation of this phenomenon under controlled conditions revealed that thermolysis caused ring opening with the loss of HCl. The product was shown by spectral and analytical data to be 2-imino-3-methyl-1-(*trans*-styryl)-imidazolidine hydrochloride (**11**).

Scheme II



Structure Proof. One problem associated with the synthetic procedure was the possibility of obtaining isomeric products from the alkylations of **1** and **6**. Two sites were available for alkylation—on the endocyclic N or on the exocyclic N. Acylations of these compounds are known to occur on the exocyclic N,[5] however, no information has appeared on their alkylation. By analogy to the 2-aminothiazolines[1] alkylation would be expected to occur on the ring, and while the nmr spectra of our compounds suggested that this was the case, the evidence was not conclusive. The structural relationships were further clouded by the fact that **1** was considerably less basic than **6**, and it was conceivable that these 2 compounds could be alkylated in different positions. We therefore wished to devise a structure proof which would unequivocally identify the site of alkylation.

During an investigation of nitroguanidine derivatives, Amos[6] and coworkers found that 1,3-dibenzyl-2-nitroimino-

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