α-Benzyltetrahydrofurfurylamines—a New Series of Psychomotor Stimulants. I

Robert L. Clarke and Louis S. Harris

Sterling-Winthrop Research Institute, Rensselaer, New York

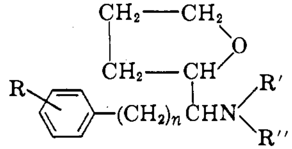
Received May 26, 1961

A series of α-benzyltetrahydrofurfurylamines has been synthesized and tested for its ability to stimulate the spontaneous activity of mice. Structure-activity relationships have been explored in detail. Some phenethylamines containing non-cyclic ether groups in the α-position were largely inactive.

In the course of our search for pharmacologically active organic compounds, we investigated a series of α-benzyltetrahydrofurfurylamines. These compounds contain a phenethylamine moiety and thus are formally related to amphetamine. Certain of these compounds were found to produce a high order of psychomotor stimulation.[1] The structure–activity relationships in this molecular system have been critically examined and are the subject of this report.

Chemistry

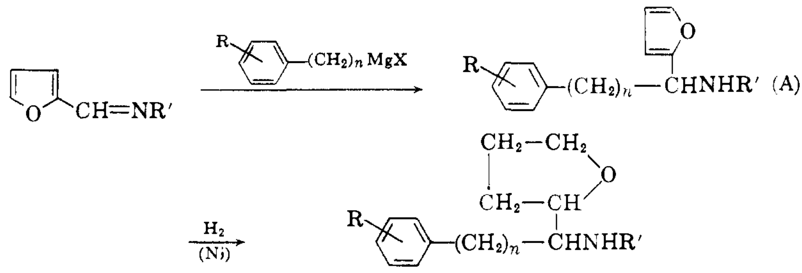
The present investigation largely concerned compounds of general structure I wherein $n = 0, 1$ or 2; R = H, F, Cl, NO_2, CH_3 or CH_3O; R′ = H or alkyl and R″ = H, alkyl, 2-methoxyethyl or cyclopropyl.



I

Compounds prepared in this series, together with two related ones, are listed in Table II. Except where otherwise noted in this table, these compounds were prepared as outlined by equation A. Two asymmetric centers in these products afford a *dl-erythro* and a *dl-*

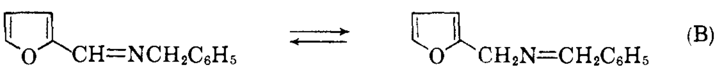
(1) Dr. Paul Long, formerly of this Institute, first observed this activity in the course of other investigations.



threo form for each compound. The basis for assignment of the *erythro* and *threo* configurations to compounds 2 and 4 of Table II will be published later. Intermediate furfurylamines are described in Table I.[2]

The reaction of furfurylidenebenzylamine with benzylmagnesium chloride to produce compound 7 of Table I (31% yield) gave as a by-product a 3.4% yield of N-benzyl-α-phenylphenethylamine hydrochloride. This compound was identified conclusively by comparison with an authetic sample prepared by Moffett and Hoehn.[3] A mixture melting point showed no depression and the infrared spectra of the two materials were identical. This hydrochloride was separated from that of the primary product by treatment of the mixture with dilute sodium hydroxide. The by-product salt was more slowly attacked due to its insolubility in water and could be filtered out.

The presence of N-benzyl-α-phenylphenethylamine among the reaction products would seem to require the presence of benzylidenebenzylamine at some stage of the reaction. In the initial reaction of furfural with benzylamine (free of benzaldehyde), there was a possibility that the furfurylidenebenzylamine might tautomerize according to equation B. Hydrolysis of the tautomerized compound under formative conditions would produce benzaldehyde which then



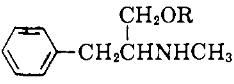
could condense with benzylamine to produce the required intermediate. However, there is no evidence that furfurylidenebenzylamine is in equilibrium with its tautomeric form, benzylidenefurfuryla-

(2) Compound 23 of Table I was prepared by Mr. Franklyn W. Gubitz of this Institute, to whom thanks are extended.

(3) R. B. Moffett and W. M. Hoehn, *J. Am. Chem. Soc.*, **69**, 1792 (1947).

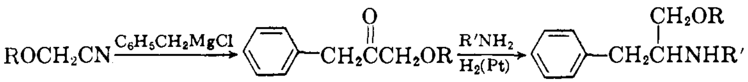
mine, for the "furfurylidenebenzylamine" at hand showed an ultraviolet absorption maximum ($E^{EtOH}_{272\ m\mu}$ = 17,900) similar to that of furfurylidenemethylamine ($E^{EtOH}_{268\ m\mu}$ = 15,900) and unlike that of benzylidenemethylamine ($E^{EtOH}_{245\ m\mu}$ = 15,400). The mode of formation of this by-product is not apparent.

The compounds of formula I have the practical disadvantage of containing two asymmetric centers with the attendant problems of diastereoisomer separation. Therefore, a second class of phenethylamines, those of general formula II and containing only one asymmetric



II

center, was prepared in an effort to maintain or enhance the stimulant activity while simplifying the chemistry involved. R is alkyl, cyclohexyl or phenyl. The compounds of this type which were studied are listed in Table IV[4] and, except where noted otherwise, they were prepared according to the method described by equation C.



(C)

Intermediate ketones, where new, are described in Table III. Simple distillation of compounds 1 and 2 in the table failed to give analytically pure products. These crude products, however, were satisfactory for subsequent reductive amination reactions. Boiling points and 2,4-dinitrophenylhydrazone derivatives of these crude products are recorded in the table.

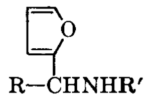
Experimental[5]

General Method for the Preparation of the Furfurylamines of Table I.—With the exception of compounds 4, 7 and 21, all the compounds of Table I were prepared by the action of the appropriate Grignard reagent on a furfurylidenealkylamine. Information on which halide was used for the Grignard reagents is contained in footnotes to the Table. Details for the preparation of furfurylidene-isopropylamine, -2-methoxyethylamine and -cyclopropylamine are given below together with preparative details for compounds 4, 7 and 21. Furfurylidene-methyl-

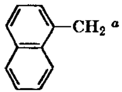
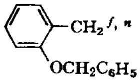
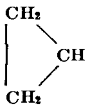
(4) Dr. Noel Albertson of this Institute kindly allowed the use of his unpublished procedure for the preparation of one of the intermediates, α-hydroxymethyl-N-methylphenethylamine.

(5) All melting points are corrected. All boiling points are uncorrected.

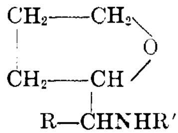
TABLE I



	R	R′	M.p. or b.p. °C.	Mm.	n^{25}_D	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
1	$C_6H_5CH_2$[a]	CH_3	86-87.3	0.5	1.5392	89	$C_{13}H_{15}NO$	77.56	77.6	7.51	7.5	6.96	7.0		
	HCl salt		116.5–119[b]				$C_{13}H_{16}ClNO$	65.68	65.8	6.79	6.4	5.89	5.9		
2	C_6H_5[c]	CH_3	125–128	8	1.5473	47	$C_{12}H_{13}NO$					7.48	7.5		
3	$C_6H_5CH_2$[a]	C_2H_5	86–91	0.3	1.5292	72									
	HCl salt[d]		178.5–181				$C_{14}H_{18}ClNO$	66.80	67.0	7.20	7.1	5.56	5.7		
4	$C_6H_5CH_2$[e,f]	CH_3	100–103	0.07											
	HCl salt		193–196.5[g]			63	$C_{14}H_{18}ClNO$	66.80	66.5	7.20	7.0			14.09	14.0
5	$C_6H_5CH_2$[a]	n-C_3H_7	99–104	0.3	1.5231	74	$C_{15}H_{19}NO$	78.57	78.3	8.35	8.1	6.10	6.1		
6	$C_6H_5CH_2$[a]	i-C_3H_7	90–92	0.1	1.5173		$C_{15}H_{19}NO$	78.57	78.4	8.35	8.6	6.10	6.3		
7	$C_6H_5CH_2$[f]	$C_6H_5CH_2$	132–139	0.04		31	$C_{19}H_{19}NO$					5.05	5.1		
	HCl salt		196–200[h,i]				$C_{19}H_{20}ClNO$	72.72	72.9	6.42	6.8	4.46	4.5		
8	$C_6H_5CH_2CH_2$[c]	CH_3	92–96	0.06	1.5332	51									
	HNO_3 salt		84–86[b]				$C_{14}H_{18}N_2O_4$	60.42	60.7	6.52	6.6	10.07	9.7		
9	$C_6H_5CH(CH_3)$[c]	CH_3	81–88	0.06	1.5340	31	$C_{14}H_{17}NO$	78.10	78.1	7.96	7.9	6.50	6.6		
10	2-$CH_3C_6H_4CH_2$[c]	CH_3	95–99	0.1	1.5397	56	$C_{14}H_{17}NO$	78.10	78.4	7.96	7.7	6.50	6.4		
11	3-$CH_3C_6H_4CH_2$[c]	CH_3	98	0.4	1.5350	71	$C_{14}H_{17}NO$	78.10	78.5	7.96	7.8	6.50	6.4		
12	4-$CH_3C_6H_4CH_2$[a]	CH_3	81–83	0.1	1.5350	57	$C_{14}H_{17}NO$	78.10	78.2	7.96	8.0	6.50	6.5		
13	4-FC_6H_4[c]	CH_3	86–90	0.5	1.5276	12	$C_{12}H_{12}FNO$	70.23	70.0	5.90	5.8	6.82	6.9		
14	4-$FC_6H_4CH_2$[a]	CH_3	104–105	0.06	1.5227	59	$C_{13}H_{14}FNO$	71.23	71.2	6.43	6.7	6.39	6.4		
15	2-$ClC_6H_4CH_2$[a]	CH_3	92–93	0.07	1.5510	80									
	HCl salt		141–143[j]				$C_{13}H_{15}Cl_2NO$					13.03[k]	13.0[k]	26.05	26.0
16	3-$ClC_6H_4CH_2$	C_2H_5	110–113	0.6		56	$C_{14}H_{16}ClNO$	67.34	67.2	6.46	6.3			14.20	14.3
17	4-$ClC_6H_4CH_2$[a]	CH_3	96–99	0.03	1.5497	77									
	HCl salt		158–160[l]				$C_{13}H_{15}Cl_2NO$					13.03[k]	13.0[k]	26.05	26.2
18	3,4-$Cl_2C_6H_3CH_2$	C_2H_5	135–138	0.3		67									
	HCl salt[d]		196–199[l]				$C_{14}H_{16}Cl_3NO$	52.45	52.6	5.03	5.0			33.18	33.1
19	2-$CH_3OC_6H_4$[c]	CH_3	98–99	0.08	1.5502	9	$C_{13}H_{15}NO_2$	71.85	71.5	6.97	7.1	6.44	6.6	14.3[m]	12.4[m]

20	4-$CH_3OC_6H_4CH_2$[a]	CH_3	112–129	0.02	1.5427	67	$C_{14}H_{17}NO_2$					6.06	6.1		
	HCl salt		140.5–142.5[j]				$C_{14}H_{16}ClNO_2$	62.97	62.4	6.77	6.8			13.24	13.2
21	C_6H_{11}[c]	CH_3	66–68	0.07	1.4941	53	$C_{12}H_{19}NO$	74.61	74.7	9.91	9.6	7.25	7.2		
22		CH_3	153–155	0.07		59									
	HCl Salt		200.5–209.5[h]				$C_{17}H_{18}ClNO$	70.94	70.8	6.30	6.2			12.32	12.1
23		CH_3	Base not isolated												
	HCl salt		174 (dec.)[g]			23	$C_{19}H_{20}ClNO_2$	69.19	68.9	6.11	6.4			10.75	10.5
24	$C_6H_5CH_2$	CH_2CH_2 | OCH_3	122–125	0.1	1.5255	70									
	HCl salt		115–117[b]				$C_{16}H_{20}ClNO_2$	63.93	64.0	7.15	7.3			12.58	12.6
25	$C_6H_5CH_2$		91–95	0.2	1.5414	23	$C_{16}H_{17}NO$	79.26	79.6	7.54	7.9	6.16	6.2		

[a] Prepared from RMgCl. [b] Recrystallized from ethyl acetate. [c] Prepared from RMgBr. [d] This salt is not very soluble in water and considerable of it precipitated as a solid when the Grignard reaction producing it was acidified. [e] This compound has two methyl groups on the nitrogen atom. [f] Preparation described separately in the Experimental Section. [g] From ethanol. [h] From water. [i] If immersed at 180°, the salt gives the indicated melting point. If immersed at 195°, it melts at once. [j] From acetone. [k] Ionic chlorine analysis. [l] From acetonitrile. [m] Methoxyl analysis. [n] See footnote 2.

TABLE II 

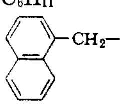
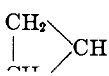
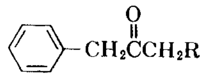
	R	R'	M.p. or B.p. °C.	Mm.	n^{25}_D	Yield, %
1	$C_6H_5CH_2$[a,i]	H	110–111	0.03	1.5241	38
1a	HCl salt		175.2–176[b,c]			8
2	$C_6H_5CH_2$[i]	CH_3	101–106	0.3		96
2a	*dl-erythro*·HCl[a]		179–180			45
2b	*dl-threo*·HCl[a]		158–160.5			9
3	C_6H_5	CH_3	Base not distilled			
3a	*dl*-isomer I·HCl[c]		238–239.5[d]			42
3b	*dl*-isomer II·HCl[c]		166–169[e]			17
4	$C_6H_5CH_2$[i]	C_2H_5	85–88	0.18	1.5151	97
4a	*dl-erythro*·HCl[a]		159.5–161[d]			26
4b	*dl-threo*·HCl[a]		151–152.5[f]			20
5	$C_6H_5CH_2$[g,i]	CH_3	107–109.5	0.9	1.5181	90
5a	HCl salt[i]		201–205.5[h]			
6	$C_6H_5CH_2$[i]	n-C_3H_7	94–102	0.16	1.5109	95
7	$C_6H_5CH_2$[i]	i-C_3H_7	98–102	0.06	1.5071	93
8	$C_6H_5CH_2$[i,l]	$C_6H_5CH_2$	214–219.5 dec.[d]			34
9	$C_6H_5CH_2CH_2$[i,l]	CH_3	103.5–115.5[j]			72
10	$C_6H_5CH(CH_3)$[i]	CH_3	82.5–85	0.02	1.5235	51
11	2-$CH_3C_6H_4CH_2$[i]	CH_3	91–97	0.09	1.5259	84
12	3-$CH_3C_6H_4CH_2$[i]	CH_3	88–98	0.09	1.5210	86
13	4-$CH_3C_6H_4CH_2$[i]	CH_3	98–99	0.27	1.5210	87
14	4-FC_6H_4[i]	CH_3	79–81	0.2	1.5068	73
15	4-$FC_6H_4CH_2$[i]	CH_3	110–113	0.4	1.5085	
16	2-$ClC_6H_4CH_2$[i]	CH_3	114–115	0.03	1.5356	80
17	3-$ClC_6H_4CH_2$[i]	C_2H_5	119–127	0.7	1.5263	59
17a	HCl salt[c]		164–166.5[d]			
18	4-$ClC_6H_4CH_2$[i,l]	CH_3	184–191.5[e]			48
19	3,4-$Cl_2C_6H_3CH_2$[i]	C_2H_5	126–132	0.03	1.5398	66
20	4-$CH_3OC_6H_4CH_2$[c,l]	CH_3	161.5–163.5[e]			47
21	4-$NO_2C_6H_4CH_2$[a,l]	C_2H_5	230–232[e,l]			
22	C_6H_{11}[i]	CH_3	68–71	0.1	1.4859	78
23	 [i,l]	CH_3	156–159			74
24	$C_6H_5CH_2$[i]	$CH_3OCH_2CH_2$	138–141	0.8	1.5126	
25	$C_6H_5CH_2$[i,m]		96–102	0.2	1.5194	46

TABLE II (*continued*)

Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
$C_{12}H_{18}ClNO$	63.29	63.3	7.97	7.9			15.57	15.7
$C_{13}H_{19}NO$	76.05	76.1	9.33	9.0	6.82	6.9		
$C_{13}H_{20}ClNO$	64.57	64.3	8.34	8.1	5.79	5.8		
$C_{13}H_{20}ClNO$	64.57	64.7	8.34	8.2	5.79	5.9		
$C_{12}H_{18}ClNO$	63.29	63.3	7.97	7.9			15.57	15.7
$C_{12}H_{18}ClNO$	63.29	63.5	7.97	7.7			15.57	15.7
$C_{14}H_{22}ClNO$	65.76	65.8	8.67	8.6			13.87	14.2
$C_{14}H_{22}ClNO$	65.76	66.1	8.67	8.7			13.87	14.2
$C_{14}H_{22}ClNO$	65.76	65.9	8.67	8.4			13.87	13.7
$C_{15}H_{23}NO$	77.22	77.3	9.93	9.8	6.00	5.9		
$C_{15}H_{23}NO$	77.22	77.0	9.93	10.0	6.00	6.1		
$C_{19}H_{24}ClNO$	71.78	71.7	7.61	7.9			11.15	11.1
$C_{14}H_{22}ClNO$	65.73	65.7	8.67	8.8			13.86	13.9
$C_{14}H_{21}NO$	76.67	76.5	9.65	9.3	6.39	6.4		
$C_{14}H_{21}NO$	76.67	76.9	9.65	9.5	6.39	6.4		
$C_{14}H_{21}NO$	76.67	76.6	9.65	9.4	6.39	6.4		
$C_{14}H_{21}NO$	76.67	76.5	9.65	9.4	6.39	6.4		
$C_{12}H_{16}FNO$	68.86	68.9	7.71	7.7	6.69	6.7		
$C_{13}H_{18}FNO$	69.92	70.0	8.12	8.2	6.27	6.2		
$C_{13}H_{18}ClNO$					5.84	5.7	14.79	14.7
$C_{14}H_{20}ClNO$							13.92	13.3
$C_{14}H_{21}Cl_2NO$					4.82	4.9	24.43	24.5
$C_{13}H_{19}Cl_2NO$			12.84[k]	12.8[k]	5.07	5.1	25.67	26.1
$C_{14}H_{19}Cl_2NO$	58.34	58.6	6.64	6.5			24.60	24.5
$C_{14}H_{22}ClNO_2$	61.86	61.5	8.61	8.4			13.05	13.1
$C_{14}H_{21}ClN_2O_3$	55.90	55.7	7.03	7.0	9.31	9.6		
$C_{12}H_{23}NO$	73.04	73.3	11.74	11.5	7.10	7.1		
$C_{17}H_{22}ClNO$	69.95	69.9	7.60	7.6			12.15	12.0
$C_{15}H_{23}NO_2$	72.26	72.3	9.29	9.2	5.61	5.6		
$C_{15}H_{21}NO$	77.88	77.6	9.15	9.3	6.05	6.2		

[a] Preparation described separately in the Experimental Section. [b] Recrystallized from acetonitrile. [c] Not known whether *threo* or *erythro* form. [d] From ethanol. [e] From acetonitrile. [f] From ethyl acetate. [g] This compound has two methyl groups on the nitrogen atom. [h] From isopropyl alcohol. [i] Probably a mixture of *erythro* and *threo* forms. [j] From acetone as spherulites or as a granular solid which reverts to spherulites on standing. [k] Ionic chlorine analysis. [l] Hydrochloride salt. [m] The cyclopropane ring apparently survived the hydrogenation reaction. The spectrum of this compound was different from those of the N-propyl and N-isopropyl compounds (6 and 7) which would have been produced by hydrogenolysis. A methyl group band at 7.25 μ was present in the N-propyl and N-isopropyl compounds but missing in the N-cyclopropyl compound.

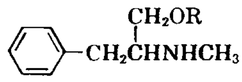
TABLE III



	R	B.p. °C.	Mm.	n_D^{25}	Yield. %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1[a,b]	—$OCH(CH_3)_2$	118–125	6	....	40	$C_{12}H_{16}O_2$	...	...	..	..
2[c,d]	—$O(CH_2)_3CH_3$	140–142	6	....	27	$C_{13}H_{18}O_2$	...	...	..	..
3[e]	—$O(CH_2)_5CH_3$	122–126	0.7	1.4916	24	$C_{15}H_{22}O_2$	76.89	76.95	9.74	9.37
4[f]	—$O(CH_2)_7CH_3$	137–140	0.5	1.4880	27	$C_{17}H_{26}O_2$	77.81	77.35	9.99	9.58
5[g,h]	—OCH_3	196–198.5	0.02	1.5068	67	$C_{13}H_{18}O_3$	70.24	70.29	8.16	7.95

[a] Prepared from isopropoxyacetonitrile, H. R. Henze, V. B. Duff, W. H. Matthews, Jr., J. W. Melton, and E. O. Forman, *J. Am. Chem. Soc.*, **64,** 1222 (1942). [b] The 2,4-dinitrophenylhydrazone derivative was prepared in a standard manner and percolated through silica gel to remove some darkly colored impurities. Recrystallization from absolute ethanol afforded yellow needles, m.p. 97.5–98.5°. *Anal.* Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.05; H, 5.41; N, 15.05. Found: C, 58.15; H, 5.32; N, 15.04. [c] Prepared from *n*-butoxyacetonitrile, C. D. Hurd and G. W. Fowler, *J. Am. Chem. Soc.*, **61,** 249 (1939). [d] The 2,4-dinitrophenylhydrazone derivative was prepared and purified as in *b* to give yellow needles, m.p. 110–112°. *Anal.* Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.06; H, 5.74; N, 14.50. Found: C, 59.16; H, 5.49; N, 14.53. [e] Prepared from *n*-hexyloxyacetonitrile as described in the Experimental Section. [f] Prepared from octyloxyacetonitrile, C. F. H. Allen and J. A. Van Allan, *J. Org. Chem.*, **14,** 754 (1949). [g] This compound has an *n*-propoxy group in the *ortho* position of the ring. [h] Prepared from methoxyacetonitrile and *o*-propoxybenzylmagnesium chloride (described in the Experimental Section).

TABLE IV



	R	M.p. of hydrochloride	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
1[a]	CH_3	111.4–113.0[bc]	62	$C_{11}H_{18}ClNO$	61.25	61.30	8.41	8.22	16.44	16.33
2[de]	CH_3	150.4–153.8[bf]	27	$C_{12}H_{20}ClNO$	...	...	13.51[g]	13.26[g]	15.44	15.46
3[hi]	C_6H_5	101.6–103.4[b]	37	$C_{11}H_{18}ClNO$	61.25	61.07	8.41	8.31	16.44	16.32
4[j]	C_2H_5	152.0–154.0[bf]	58	$C_{12}H_{20}ClNO$	62.71	62.61	8.77	8.69	15.43	15.48
5	$CH(CH_3)_2$	160.4–162.6[bk]	45	$C_{13}H_{22}ClNO$	64.04	63.97	9.10	9.03	14.54	14.61
6[lm]	$CH(CH_3)_2$	94.0–96.4[no]	29	$C_{14}H_{24}ClNO_2$	61.41	61.08	8.84	8.67	12.95	13.01
7	$(CH_2)_3CH_3$	128.2–130.4[bk]	49	$C_{14}H_{24}ClNO$	65.22	65.07	9.38	9.49	13.75	13.72
8	$(CH_2)_5CH_3$	105.4–107.2[nk]	42	$C_{16}H_{28}ClNO$	67.21	67.30	9.87	9.60	12.40	12.35
9	$(CH_2)_7CH_3$	111.4–113.8[bk]	33	$C_{18}H_{32}ClNO$	68.87	68.83	10.28	10.16	11.30	11.19
10[p]	$CH(CH_2)_5$	130.0–133.0[bk]	71	$C_{16}H_{26}ClNO$	67.71	67.50	9.24	9.30	12.49	12.46
11[q]	C_6H_5	162.0–163.4[ro]	21	$C_{16}H_{20}ClNO$	69.17	69.28	7.26	7.34	12.76	12.82
12[s]	CH_3	73.2–75.2[to]	43	$C_{14}H_{24}ClNO_2$	61.41	61.11	8.84	8.88	12.95	12.97

[a] The precursor, 1-methoxy-3-phenyl-2-propanone, is described by M. Darmon, *Compt. rend.*, **197**, 1328 (1933). [b] From acetone. [c] Spherulites. [d] This compound has two methyl groups on the nitrogen atom. [e] This compound was prepared from N,N-dimethyl-α-hydroxymethylphenethylamine; see Experimental section. [f] Plates. [g] Methoxyl analysis. [h] This compound has two hydrogen atoms on the nitrogen atom. [i] See the Experimental section for the special preparation of this compound. [j] The precursor, 1-ethoxy-3-phenyl-2-propanone, is described by H. R. Henze, G. L. Sutherland and G. D. Edwards, *J. Am. Chem. Soc.*, **73**, 4915 (1951). [k] Blades. [l] This compound has a β-hydroxyethyl group in place of the methyl group on the nitrogen atom. [m] Five equivalents of ethanolamine were used here instead of the methylamine described in the general procedure. [n] From ethyl acetate. [o] Needles. [p] The precursor, 1-cyclohexyloxy-3-phenyl-2-propanone, is described by L. Palfray and S. Sabetay, *Bull. Soc. Chim. France*, **43**, 900 (1928). [q] The precursor, 1-phenoxy-3-phenyl-2-propanone, is described by P. Pfeiffer and H. Epler, *Ann. Chem.*, **545**, 263 (1940). [r] From acetonitrile. [s] This compound has an *n*-propoxy group in the *ortho* position of the ring. [t] From benzene–ether.

amine, -ethylamine and -*n*-propylamine are known.[6]

The Grignard reagents were prepared from 0.3 mole of the appropriate alkyl, aralkyl, or aryl halide and 0.35 mole of magnesium powder in ether, using a reaction time under reflux of 1.5 hr. (The phenylmagnesium bromide was given 6 hr. to form.) To these Grignard reagents was added 0.23 mole of furfurylidenealkylamine in ether and reflux was continued for 1 hr. This mixture was treated with 250 ml. of 4 *N* hydrochloric acid and the water layer was separated, made strongly alkaline, and subjected to steam distillation. The product was extracted from the distillate with ether and distilled.

Furfurylideneisopropylamine.—Furfural (48 g., 0.5 mole) was added dropwise with stirring to 32.5 g. (0.55 mole) of isopropylamine, the temperature of the reaction mixture being maintained between 15 and 20°. The mixture was stirred for 1.5 hr. and then saturated with sodium hydroxide. The product was extracted from this mixture with ether; the extract was dried over solid sodium hydroxide and concentrated to a residue. Distillation of the residual oil afforded 65.2 g. (96% yield) of the desired product, b.p. 72–74° (11 mm.), n^{25}_{D} 1.5023.

Furfurylidene-2-methoxyethylamine.—Furfural (32 g., 0.33 mole) was allowed to react with 115 g. of 65% aqueous 2-methoxyethylamine (1.0 mole) in the manner described immediately above to give 45.8 g. (90% yield) of the desired product, b.p. 64–65° (0.7 mm.).

Furfurylidenecyclopropylamine.—Furfural (26.2 g., 0.27 mole) was allowed to react with 67 g. of 30% aqueous cyclopropylamine (0.35 mole) in the manner described above for the preparation of furfurylideneisopropylamine. The product 32.4 g. (89% yield), boiled at 71–72° (6 mm.).

α-Benzyl-N,N-dimethylfurfurylamine.—A solution of 15 g. (0.075 mole) of α-benzyl-N-methylfurfurylamine in 21 g. of formic acid and 15 g. of 40% aqueous formaldehyde was heated at 100° for 1 hr. This mixture was distilled and the product collected. See compound 4, Table I, for further data.

N,α-Dibenzylfurfurylamine.—Benzylmagnesium chloride was prepared from 114 g. (0.9 mole) of benzyl chloride and 26.7 g. (1.1 mole) of magnesium powder in 600 ml. of ether. The Grignard reagent was given 2 hr. at reflux to form, and was then treated with 112.5 g. (0.61 mole) of furfurylidenebenzylamine[7] in 500 ml. of ether at a rate to give controlled reflux. The mixture was refluxed for 1 hr., left overnight, then hydrolyzed with 800 ml. of 2 *N* hydrochloric acid. The solid material was collected and made strongly alkaline with 2 *N* sodium hydroxide. The resulting mixture of oil, water, and solid with added ether was filtered immediately. The solid material, N-benzyl-α-phenylphenethylamine hydrochloride, after two recrystallizations from alcohol and one from water, melted at 246–251° (uncorr.) (6.9 g., 3.4%). An additional recrystallization from water raised the melting point to 249–252° (uncorr.); reported,[3] 245–249°.

Anal. Calcd. for $C_{21}H_{22}ClN$: C, 77.87; H, 6.85; Cl, 10.95; N, 4.32. Found: C, 77.55; H, 6.99; Cl, 10.81; N, 4.29.

The ether layer from the filtration above was distilled to give the desired furfurylamine, Compound 7 of Table I.

(6) B. L. Emling, J. E. Beatty, and J. R. Stevens, *J. Am. Chem. Soc.*, **71**, 703 (1949).
(7) R. L. Hinman and K. L. Hamm, *J. Org. Chem.*, **23**, 529 (1958).

α-(*o*-Benzyloxyphenyl)-N-methylfurfurylamine Hydrochloride.[2]—*n*-Butyllithium was prepared from 4.3 g. (0.62 mole) of lithium wire and 34.3 g. (0.25 mole) of *n*-butyl bromide in 100 ml. of ether at −10° in 3 hr. The ethereal solution, after filtration, was added dropwise with stirring to a solution of 52.6 g. (0.2 mole) of benzyl 2-bromophenyl ether[8] in 300 ml. of ether and the resulting mixture was refluxed for 1 hr. To this stirred mixture was added 11 g. (0.1 mole) of furfurylidenemethylamine[6] dissolved in 100 ml. of ether. After a 2 hr. reflux period the excess alkyllithium was decomposed by water. The mixture was acidified with dilute hydrochloric acid, cooled, and the supernatant liquids decanted from a heavy, red, viscous oil. This oil was dissolved in water by warming and the solution was washed with ether. Basification of this solution and extraction of the product with ether gave a red oil which formed a brown, solid hydrochloride salt (6.8 g., 23%), m.p. 178° (dec.). This salt was recrystallized three times from alcohol to give 4.6 g. of tan crystals, m.p. 174° (dec.). See Compound 23, Table I, for further data.

General Method for the Preparation of the Tetrahydrofurfurylamines of Table II.—Hydrogenation of the furfurylamines of Table I was accomplished in alcohol in the presence of W-4 Raney nickel catalyst at room temperature in from 2 to 6 hr. under a hydrogen pressure of approximately 100 atm. A temperature of 60° was necessary to produce compound 20 in the table. Approximately one teaspoonful of catalyst was used for each 0.1 mole of furfurylamine. The catalyst and solvent were removed and the residual oil was either distilled or converted directly to its hydrochloride salt as indicated in the table. Generally, no effort was made to separate and purify both isomers.

In the case of Compound 3 in Table II (a 0.08 mole run), the residual oil from the hydrogenation was treated with one equivalent of ethereal hydrogen chloride and the precipitated salt recrystallized from 800 ml. of acetonitrile to give crude Isomer I. Concentration of the filtrate to a 10 ml. volume gave a second crop of this isomer. Dilution of the filtrate from the second crop with 20 ml. of ether precipitated Isomer II.

α-Benzyltetrahydrofurfurylamine (I, $n = 1$, R = R′ = R″ = H).—A mixture of 50.3 g. (0.27 mole) of benzyl furyl ketone (prepared in 89% yield, b.p. 109–115° (0.08 mm.), n^{25}_D 1.5800 by the method of Borsche *et al.*,[9] 35 g. (0.32 mole) of benzylamine, 650 ml. of methanol and 2 teaspoonfuls of Raney nickel was treated with hydrogen under 147.6 kg./cm.^{2} for 6 hr. at 150°. The mixture was filtered and the solvent removed from the filtrate *in vacuo*. The residue was dissolved in ether and the basic product extracted from this solution with dilute hydrochloric acid. The acid extracts were made basic with sodium hydroxide and the liberated base was extracted with ether. The ether extract was washed with saturated salt solution, dried over sodium sulfate and concentrated to a residue. The residual oil was distilled to give the product described as Compound 1, Table II.

dl-erythro- **and** *dl-threo-*α**-Benzyl-N-methyltetrahydrofurfurylamine.**—To 135 g. (0.67 mole) of the oily mixture of diastereoisomers of α-benzyl-N-methyltetrahydrofurfurylamine (Compound 2 of Table II) was added 350 ml. of ether and 110

(8) R. C. Huston, A. Neeley, B. L. Fayerweather, H. M. D'Arcy, F. H. Maxfield, M. M. Ballard, and W. C. Lewis, *J. Am. Chem. Soc.*, **55**, 2146 (1933).

(9) W. Borsche, H. Leditschke, and K. Lange, *Chem. Ber.*, **71**, 957 (1938).

ml. of 6.3 *N* alcoholic hydrogen chloride. The 118 g. of solid which precipitated was filtered immediately and recrystallized twice from absolute alcohol to give 72.6 g. of the *dl-erythro* salt, m.p. 179–180°. This product precipitated from the solvent initially in the form of needles which then reverted to plates on standing. It is Compound 2a, Table II.

The filtrate from separation of the *erythro* isomer, upon standing at 25° slowly deposited 19.3 g. of massive prisms of the *dl-threo* salt. This solid was dissolved in 20 ml. of alcohol and precipitated by adding 60 ml. of ethyl acetate, to give 14.3 g. of the pure isomer, m.p. 158–160.5° (Compound 2b, Table II).

dl-erythro- **and** *dl-threo-α-***Benzyl-N-ethyltetrahydrofurfurylamine.**—To 113 g. (0.515 mole) of α-benzyl-N-ethyltetrahydrofurfurylamine was added with cooling 31 ml. of 8.3 *N* alcoholic hydrogen chloride (0.26 mole). The mixture was set in the refrigerator for 2 hr., the cake which formed was broken apart, 200 ml. of ether was added and the mixture was quickly stirred and filtered. The impure *dl-erythro* hydrochloride which separated, 60 g., m.p. 129–152°, was recrystallized three times from a volume in ml. of absolute alcohol numerically equal to the weight in grams of the solid to give 33.2 g. of pure *dl-erythro* salt (Compound 4a, Table II).

The filtrate from separation of the *dl-erythro* hydrochloride was warmed on the steam-bath to remove the ether and treated with cooling with 31 ml. of 8.3 *N* alcoholic hydrogen chloride. The mixture was set in the refrigerator for 3 hr. to complete the precipitation. The solid was filtered and washed with 1:1 alcohol–ether to give 46 g. of crude *dl-threo* hydrochloride. The salt was recrystallized by dissolving it in 1500 ml. of ethyl acetate, concentrating the solution to 600 ml. and allowing the product to crystallize without stirring and with cooling only to room temperature. This solid, 31.6 g., m.p. 140–147°, was recrystallized twice more from ethyl acetate to give 26.1 g. of pure *dl-threo* salt (Compound 4b, Table II).

*dl-erythro-***N-Ethyl-***α-*(*p*-**nitrobenzyl)-tetrahydrofurfurylamine Hydrochloride.**—A solution of 10 g. (0.045 mole) of *dl-erythro-α*-benzyl-N-ethyltetrahydrofurfurylamine in 30 ml. of concentrated sulfuric acid was added with stirring to a mixture of 20 ml. each of concentrated sulfuric and nitric acids, the temperature of the reaction mixture being held at 5–10°. The mixture was then held at this temperature for 1.5 hr. and poured onto 500 g. of cracked ice. Basification of the mixture with 35% aqueous sodium hydroxide, extraction of the liberated base with ether, washing the ether extract with saturated salt solution, drying the solution over sodium sulfate and removal of the solvent gave an oily nitrated product. This oil was treated with 7.5 ml. of 9 *N* alcoholic hydrogen chloride and diluted with ether. The precipitated hydrochloride salt was collected and recrystallized from acetonitrile to give 5.3 g. (39% yield) of yellow crystals, m.p. 221–229°. A single further recrystallization gave the material described as Compound 21, Table II.

General Method for Preparation of the Ketones of Table III.—The ketones listed in Table III were prepared by the reaction of benzylmagnesium chloride (or, in one case, *o*-propoxybenzylmagnesium chloride) with the appropriate nitrile. The nitriles used are recorded in footnotes to the Table. The Grignard reagents were prepared by adding 0.32 mole of the benzyl chloride to 0.35 mole of magnesium powder in 250 ml. of ether, and refluxing the mixture for 1 hr. To the Grignard reagent was added 0.25 mole of the appropriate nitrile in 75 ml. of ether. (These proportions were maintained for larger or smaller runs.) The mixture was refluxed for 1 hr., 175 ml. of 2 N hydrochloric acid added, and this mixture stirred vigorously for 30 min. The layers were separated, the ether layer dried (Na_2SO_4), the solvent removed, and the residual oil distilled. Generally, large still-pot residues remained.

α-Chloro-*o*-tolyl-*n*-propyl Ether (*o*-Propoxybenzyl Chloride).—A solution of 26.7 g. (0.16 mole) of *o*-propoxybenzyl alcohol[10] in 75 ml. of dry ether at 0° was saturated with hydrogen chloride. This solution was kept cold for 2 hr. and at room temperature overnight. The mixture was distilled and the product (15.8 g., 53.5%) collected at 110–111.5° (8 mm.), n^{25}_D 1.5281.

Anal. Calcd. for $C_{10}H_{13}ClO$: C, 65.02; H, 7.09; Cl, 19.20. Found: C, 64.9; H, 7.2; Cl, 19.3.

Chloromethyl *n*-Hexyl Ether.—A mixture of 80 g. (0.79 mole) of *n*-hexyl alcohol and 65 g. of 35% formaldehyde was cooled in an ice-bath and saturated with hydrogen chloride. This mixture was kept cold for 3 hr. and at room temperature overnight. The layers were separated and the organic layer was distilled. The desired product (84 g., 71%) boiled at 54–56° (6 mm.), n^{25}_D 1.4278. This slightly impure product was used without further treatment.

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.79; H, 10.03; Cl, 23.53. Found: C, 56.27; H, 10.16; Cl, 22.94.

***n*-Hexyloxyacetonitrile.**—To 30.1 g. (0.34 mole) of cuprous cyanide stirred dry on a steam-bath was added 43.4 g. (0.29 mole) of chloromethyl *n*-hexyl ether in 20 min. Heating and stirring were continued for 30 min. The cooled mixture was diluted with 75 ml. of ether, filtered, and the filtrate distilled. The product (26.8 g., 66%) boiled at 86–88° (6 mm.), n^{25}_D 1.4187.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.05; H, 10.71; N, 9.92. Found: C, 68.07; H, 10.62; N, 9.85.

General Method for the Preparation of the Amines of Table IV.—Except where specified otherwise in a footnote, the compounds of Table IV were prepared by treatment of the appropriate ketone (0.04 to 0.09 mole) and 8 equivalents of methylamine in 300 ml. of absolute alcohol with hydrogen under 4 atm. pressure at room temperature in the presence of 0.3 g. of platinum oxide catalyst. Hydrogen absorption usually was complete in from 2 to 5 hr. The catalyst was separated and the filtrate freed from solvent. Treatment of the residual oil in ether with ethereal hydrogen chloride gave the desired salt.

α-Hydroxymethyl-N-methylphenethylamine.[4]—To a stirred suspension of 90 g. (0.5 mole) of N-formyl-β-phenylalanine[11] in 1 l. of tetrahydrofuran was added a solution of 38 g. (1 mole) of lithium aluminum hydride in 750 ml. of tetrahydrofuran at a rate which produced controlled reflux. This addition required 45 min. This mixture was refluxed for 2 hr. and treated dropwise with 90 ml. of water. Addition of this amount of water and then a 30 min. stirring period transformed the inorganic salts into an easily filterable form. The mixture was filtered and the

(10) M. Hart and A. D. Hirschfelder, *J. Am. Chem. Soc.*, **43**, 1688 (1921).
(11) E. Fischer and W. Schoeller, *Ann. Chem.*, **357**, 2 (1907).

filtrate freed from solvent. Trituration of the residual oil with ether furnished 48 g. (58%) of the desired amine, m.p. 67.5–69.5°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.70; H, 9.15; N, 8.48. Found: C, 72.69; H, 8.87; N, 8.31.

N,N-Dimethyl-α-hydroxymethylphenethylamine has been reported without yield data by Karrer[12] from N,N-dimethyl-β-phenylalanine ethyl ester by sodium–ethanol reduction. A solution of 16.5 g. (0.1 mole) of α-hydroxymethyl-N-methylphenethylamine in 100 ml. of 90% formic acid and 40 ml. of 35% formaldehyde was heated on the steam-bath for 2 hr. Solvent and excess reagents were removed by warming *in vacuo* and the residual oil refluxed with 50 ml. of concentrated hydrochloric acid for 1.5 hr. to hydrolyze any formate ester of the product which had formed. The acid was removed by warming *in vacuo.* The residual oil was made strongly basic with 35% sodium hydroxide, the free base extracted with ether, and the extract distilled. The product (15.3 g., 85%) boiled at 84–86.5° (0.04 mm.), n^{25}_D 1.522; reported,[12] 151° (14 mm.).

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.68; H, 9.56; N, 7.81. Found: C, 73.82; H, 9.51; N, 7.72.

N,N-Dimethyl-α-methoxymethylphenethylamine.—Sodium hydride (1.68 g., 0.07 mole) was added to a solution of 6.7 g. (0.037 mole) of N,N-dimethyl-α-hydroxymethylphenethylamine in 100 ml. of toluene and the mixture refluxed with stirring for 40 min. Dimethyl sulfate (6.3 g., 0.05 mole) was added and reflux continued for 10 min. The mixture was cooled, diluted with 40 ml. of water, and the resulting layers were separated. The product was extracted from the organic layer with dilute hydrochloric acid and the acid extract made strongly alkaline with 35% sodium hydroxide. The liberated base was taken up in ether and this solution treated with an ethereal solution of hydrogen chloride to precipitate the **hydrochloride salt** of the desired phenethylamine. For further details, see Compound 2, Table IV.

α-Ethoxymethylphenethylamine.—A mixture of 10 g. (0.056 mole) of 1-ethoxy-3-phenyl-2-propanone (see footnote *j*, Table IV), 135 ml. of 3.5% methanolic ammonia, and one-half teaspoonful of Raney nickel catalyst was subjected to 66.8 kg./cm.^{2} hydrogen pressure at 45° for 1 hr. The catalyst and solvent were removed and the residual oil treated with ethereal hydrogen chloride. The product is described as Compound 3, Table IV.

Pharmacology

Method.—The spontaneous activity of mice was measured by a modification[13] of the method of Dews.[14] The apparatus consisted of a round metal box 40 cm. in diameter with a wire mesh bottom and Lucite top. A beam of light passing across one diameter impinged on a photoelectric cell so adjusted that a mouse breaking the light path ac-

(12) P. Karrer, *Helv. Chim. Acta*, **4**, 76 (1921).
(13) L. S. Harris and F. C. Uhle, *J. Pharmacol.*, **132**, 251 (1961).
(14) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

tivated a magnetic counter. Male albino mice (18–28 g.) were used one time only. They were allowed free access to food and water until placed in the activity cage. The drugs, dissolved in distilled water, were given intraperitoneally. All dosages are expressed in terms of drug base. Groups of five mice were medicated, placed in the activity cage, and given 10 min. in which to adjust to the environment. Then the number of interruptions of the light beam by the mice was recorded for a 30 min. period. A minimum of two groups per dose at four dose levels were run. Control groups receiving distilled water were run each day.

The data are recorded as threshold dose, dose producing maximum effect, maximum "count" obtained, and the ratio of the maximum count to that of water controls. The control count utilized for this ratio was the mean of the pooled sample of all controls (160) obtained in this laboratory during the period this study was in progress.

Results.—The results are shown in Table V. If the α-methyl group of amphetamine is replaced by a 2-tetrahydrofurfuryl group, compound II-1 is obtained, (*i.e.*, Table II—compound 1), which can be considered as the parent compound of the present series. Introduction of this group also creates a second asymmetric center in the molecule and two diastereoisomeric forms are then possible. In three cases, compounds II-2, 3 and 4, these diastereoisomeric pairs have been separated and tested.

The activity of the parent compound, α-benzyltetrahydrofurfurylamine (II-la), was markedly less than that of *dl*-amphetamine. Methylation of the nitrogen atom of this compound, however, greatly increased its activity. This methylated compound, II-2, was separated into its *erythro* (II-2a) and *threo* (II-2b) forms. The *threo* compound was about twice as active as the *erythro* compound and had an activity equivalent to that of *dl*-amphetamine. This is illustrated in Fig. 1 where the log–dose response curves for both II-2b and *dl*-amphetamine are plotted. The curves are so nearly superimposable that II-2b data had to be displaced by half a unit in order to make the graph legible.

When the methyl group on the nitrogen atom of II-2 was replaced by an ethyl group, the activity was nearly doubled. Again *erythro* (II-4a) and *threo* (II-4b) forms were isolated and the *threo* form proved to be the more active.

A further increase in the length of the alkyl group on the nitrogen

TABLE V

EFFECT OF VARIOUS PHENETHYLAMINE ETHERS ON THE SPONTANEOUS ACTIVITY OF MICE

Compound — Table	Compound — Cpd.	Threshold dose mg./kg.	Dose for maximum effect mg./kg.	30 Minute "count" at maximum dose	Ratio of maximum count to control count
H_2O				258	1
dl-Amphetamine		2	32	1015	3.93
I	1		No stimulation		
II	1a	8	64	481	1.83
II	2a	4	32	844	3.27
II	2b	2	32	1068	4.13
II	3a	8	64	905	3.51
II	3b	4	64	644	2.49
II	4a	2	32	963	3.70
II	4b	1	16	1027	3.97
II	5a	8	32	760	2.95
II	6	4	32	819	3.18
II	7	8	64	832	3.36
II	8		No stimulation		
II	9	3	30	468	1.82
II	10	3	30	460	1.78
II	11		No stimulation		
II	12	8	32	538	2.08
II	13	16	128	742	2.88
II	14[a]	8	32	649	2.52
II	15	8	64	593	2.30
II	16		No stimulation		
II	17a	4	32	914	3.54
II	18	4	32	889	3.45
II	19	2	32	1162	4.50
II	20		100	644	2.50
II	21	32	64	490	1.90
II	22		No stimulation		
II	23		No stimulation		
II	24		64	467	1.81
II	25	8	32	1014	3.94
IV	1		No stimulation		
IV	3		64	438	1.70
IV	4	4	8	470	1.82
IV	5		No stimulation		
IV	6		No stimulation		
IV	7		No stimulation		
IV	11		No stimulation		
IV	12		No stimulation		

[a] This compound was given orally.

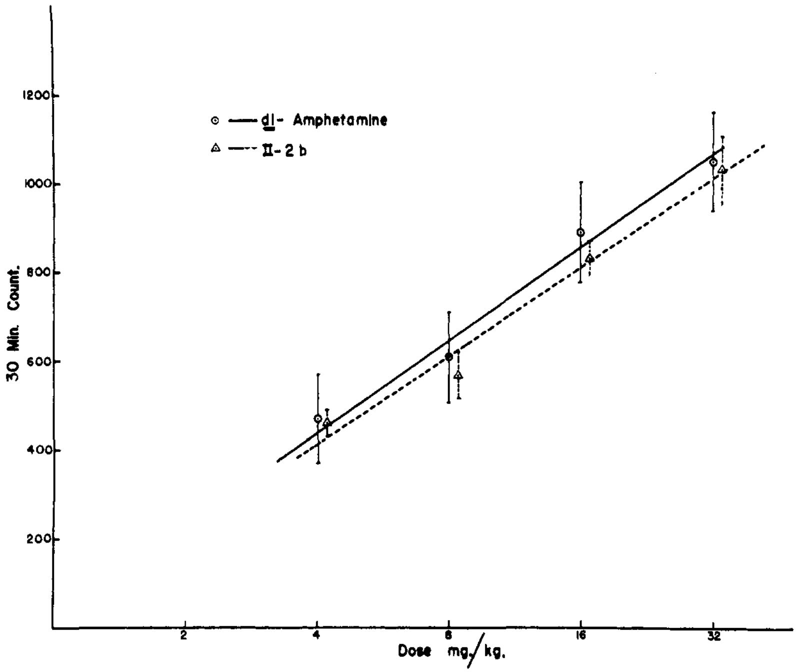


Fig. 1.—A comparison of the effects of *dl*-amphetamine and *dl-threo*-α-benzyl-N-methyltetrahydrofurfurylamine (II-2b) on the spontaneous activity of mice. Since the two curves are nearly superimposable, the II-2b data have been shifted half a unit to the right.

atom produced less active compounds, *cf.* *n*-propyl (II-6) and isopropyl (II-7), as did dialkylation (II-5a). The N-cyclopropyl derivative (II-25), however, had an activity equivalent to that of the N-methyl compound. Attachment of an ether function, 2-methoxyethyl (II-24), to the nitrogen led to a greater decrease in activity while the N-benzyl compound (II-8) was devoid of activity.

The furfuryl ring in this series must be saturated to obtain stimulation. For instance, the unsaturated analog I-1 of the N-methyl compound II-2 produced no psychomotor stimulation.

Decreasing the chain length between the phenyl group and the amine nitrogen (compounds II-3a, 3b, and 14) decreased but did not eliminate activity. This is of interest since these compounds depart from the C_6H_5–C–C–N structure usually considered necessary for central activity. Branching in this chain connecting the phenyl and the amino groups (compound II-10) and lengthening it to three methylene groups (compound II-9) produced a more profound decrease in activity.

All monosubstitution in the phenyl ring (Compounds II-11, 12, 13, 14, 15, 16, 17a, 18, 20 and 21) lessened the stimulatory activity, this effect being most pronounced with 2-substituents (compounds II-11 and 16). A chlorine atom at the 3- or 4-position (II-17a and 18), however, lowered the activity of the compound only slightly and, indeed, the preparation of a 3,4-dichloro derivative (II-19) resulted in an *erythro–threo* mixture with activity at least as great as that of the parent compound. Reduction of the phenyl ring to a cyclohexyl group (II-22) or replacement of it by a 1-naphthyl group (II-23) eliminated activity.

In an attempt to avoid the chemical difficulties imposed by the two asymmetric centers of the tetrahydrofurfuryl compounds described above, a series of simple alkyl ethers was prepared (Table IV). Of the compounds tested in this series, only the ethyl ethers, IV-3 and 4, had an appreciable stimulating effect. Thus, the tetrahydrofurfuryl group seems to confer a degree of specificity on the molecule.

In anaesthetized cats both the N-methyl (II-2b) and N-ethyl (II-4b) tetrahydrofurfuryl derivatives had less than 1/10 the cardiovascular activity of *dl*-amphetamine. Tachyphylaxis was easily elicited with either compound.

Discussion.—With the exception of the tetrahydrofurfuryl group, replacement of the α-methyl group of amphetamine by various alkyl ether groups led to a marked decrease in central stimulating activity.

Within the tetrahydrofurfuryl series (formula I), certain structure-activity relationships emerged which differed from those in the amphetamine series. With regard to alkylation of the nitrogen atom, peak activity in the present series was achieved when the alkyl group was ethyl. In the amphetamine series a methyl group produced peak activity.[15] It is of interest to note that the N-cyclopropyl derivative, II-25, had a high degree of activity. In the present series, shortening the chain length between the phenyl and the amine group did not cause the profound decrease in activity accompanying a similar change

(15) A. N. Novelli and M. L. Tainter, *J. Pharmacol.*, **77**, 324 (1943).

in the amphetamine series.[16] Ring substitution, in general, produced changes which were similar to those observed with amphetamine.[16] However, the relatively small decrease in activity produced by *m*- or *p*-halogenation (*cf.* II-15, 17a, and 18) was unexpected as was the preservation of activity in the N-ethyl-3,4-dichloro compound, II-19. We have since found an analogous case wherein 1-(3,4-dichlorophenyl)-2-isopropylaminoethanol produced a degree of stimulation unobtainable with the unhalogenated compound.

It is surprising that none of the simple ethers (Table IV) was very active. This is particularly true of compounds IV-4, 5, and 7 which closely approximate the active tetrahydrofurfuryl derivative II-2. The tetrahydrofurfuryl ring system, therefore, gives a degree of specificity to the molecule which is difficult to reconcile with physical properties such as solubility, dissociation characteristics or hydrogen bonding. It might be postulated that this ether ring enhances the affinity or fit of the phenethylamine structure to the receptor.

Further chemical and pharmacological studies with this interesting series of compounds are in progress and will be reported at a later date.

Acknowledgments.—The authors wish to thank Mrs. G. A. Snyder and Miss J. R. Dembenski for technical assistance with the chemical and biological work respectively. They also thank the Physical and Analytical Sections of this Institute for spectral and analytical data.

(16) J. W. Schulte, E. C. Reif, J. A. Bacher, Jr., W. S. Lawrence, and M. L. Tainter, *J. Pharmacol.*, **71**, 62 (1941).