(20 g.) was added and the stirring and warming continued for an additional 30 min. The hot solution was filtered, the filtrate cooled with ice and made alkaline with ammonia. The mixture was extracted with chloroform; the extract was washed with saturated sodium chloride solution, dried over sodium sulfate and taken to dryness *in vacuo*. The resultant dark viscous oil was chromatographed on a Woelm no. 1 neutral alumina column (125 g., 2.5 cm. diameter) prepared in benzene and using benzene as eluent. The product was obtained as a pale yellow oil, which was crystallized from 6 *N* aqueous hydrochloric acid as a powdery white solid (7.73 g., 50.1%). Recrystallization from methanol–ethyl acetate yielded an analytical sample, m.p. 255° dec. as white needles; λ_{max}^{EtOH} 270 mμ (log ε 4.27), 282 mμ (shoulder log ε 4.19).

Anal. Calcd. for $C_{17}H_{18}ClN$: C, 75.13; H, 6.68; N, 5.15; Cl, 13.05. Found: C, 75.12; H, 6.46; N, 4.95; Cl, 13.25.

Pschorr Ring Closure Using Precursor Obtained with Tin–Hydrochloric Acid.[21]—Nine runs were made, which were combined at the indicated point for product isolation. To a cold stirred mixture of dihydrochloride [10.0 g., 0.032 mole, using the assumption that it is a 1:1 mixture of 1-(2-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride and the corresponding (1-(5-chloro-2-aminobenzyl) compound], ice (100 g.), sulfuric acid (5 ml.), and water (145 ml.) there was added gradually a solution of sodium nitrite (2.14 g., 0.031 mole) in water (15.5 ml.). The solution was kept at 0° for 1 hr.; copper powder (10 g.) was added and the mixture kept at 0° for 1 hr. and then at 26° for 20 hr. The mixture was filtered and the collected solid and the resulting liquid filtrate were processed separately. In our hands, it was convenient to combine at this stage the products of 9 identical experiments. The solid material was suspended in ammoniacal aqueous ether and then filtered; any insoluble residue was discarded. The ether layer was separated and the aqueous solution was extracted repeatedly with fresh ether. The combined ethereal extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* yielded a pinkish, crystalline product (16.1 g.). Recrystallization from methylene chloride–95% ethanol produced an analytical sample as white prisms, m.p. 125.5–126.5°; λ_{max}^{EtOH} 276 mμ (log ε 4.35), 304 mμ (shoulder, log ε 3.65).

Anal. Calcd. for $C_{17}H_{16}ClN$: C, 75.71; H, 5.93; N, 5.19; Cl, 13.14. Found: C, 75.70; H, 6.14; N, 5.31; Cl, 13.27.

The filtrate was treated with zinc dust (45 g.) and hydrochloric acid (125 ml.), vigorously heated on the steam bath for 20 min., filtered and made alkaline with aqueous ammonia. The mixture was extracted with ether and the organic extract washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* yielded a viscous oil (16.7 g.). No pure compound was isolable from this material by chromatographic or crystallization procedures.

Acknowledgment.—We wish to thank Dr. I. J. Pachter for some preliminary experimentation and helpful discussions and to acknowledge the skillful technical assistance of Mr. H. Farber.

Reserpine Analogs; Phenethylamine Derivatives[1]

A. LINDNER, V. CLAASSEN, TH. W. J. HENDRIKSEN, AND T. KRALT

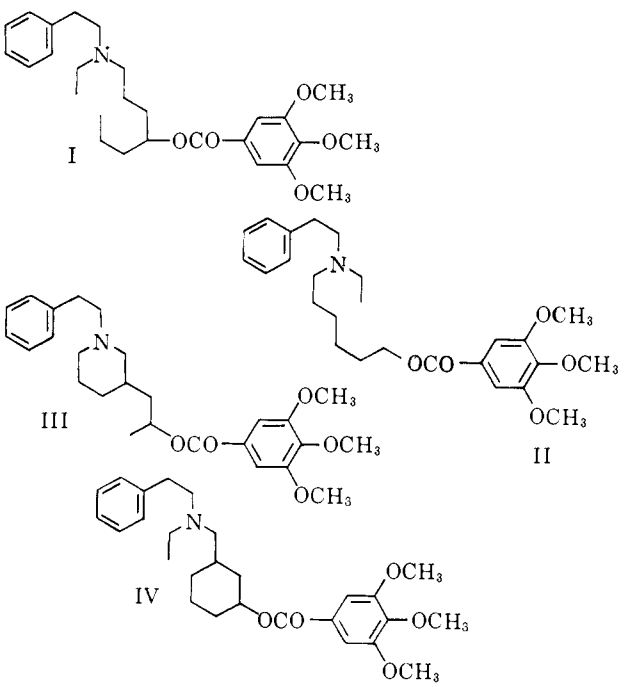
Laboratory for Experimental Pathology, University of Vienna; N.V. Philips-Duphar Research Laboratories, Weesp, The Netherlands

Received April 14, 1962

The pharmacological properties of reserpine analogs containing phenethylamine moieties are described. The most interesting pharmacological effects found are blood pressure depression, spasmolysis and adrenolysis. A discussion is given of the structure–activity relationship. A new class of spasmolytics is described with other structure–activity relationships than normally found in aminoalkyl esters.

The natural alkaloid reserpine shows various interesting pharmacological actions.[2] It was of interest to investigate which, if any, pharmacological properties of reserpine are retained in compounds that are simplified models of this alkaloid. In previous publications[1a,b] we have given a survey of the literature of the synthesis of reserpine analogs. We also have given the reasons why we have prepared phenethylamine derivatives in which some features of the reserpine structure are retained. The synthesis and the physical data of those new compounds have been described in detail.[1c] This article now describes the pharmacological investigations of these compounds and their structure–activity relationships. The compounds described may be considered as derivatives of four basic structures (I–IV). They differ in many respects from reserpine, but all contain the phenethylamine structure.

These four basic structures were varied by substituting several groups in the phenyl group, a hydroxyl group at the β-carbon atom (β-phenylethanolamines) and a methyl group at the α-carbon atom (β-phenyl-

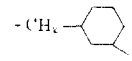
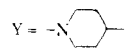
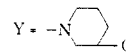
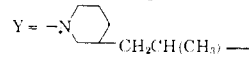


(1) (a) T. Kralt, H. D. Moed, V. Claassen, Th. W. J. Hendriksen, A. Lindner, H. Selzer, F. Brücke, G. Hertting, and G. Gogolak, *Nature*, **188**, 1108 (1960); (b) T. Kralt, W. J. Asma, H. H. Haeck, and H. D. Moed, *Rec. trav. chim.*, **80**, 313 (1961); (c) T. Kralt, W. J. Asma, and H. D. Moed, *ibid.*, **80**, 330, 431, 932 (1961).

(2) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, Toronto, 1957.

TABLE I

Active Depressants

	Compounds $C_6H_5(CH_2)_2N(C_2H_5)YOCOC_6H_2(OCH_3)_3$-3,4,5 Y	A.D.C.[3] (rat)	A.D.C.[3] (cat)	Adrenolytic activity Cpd. 53 = 1 (1/20 D.H.E.T.)	Spasmolytic activity, guinea pig ileum Carbamylcholine (Papaverine = 1)	Spasmolytic activity, guinea pig ileum $BaCl_2$ (Papaverine = 1)	LD_{50} i.p. mg./kg. (mice)
1	$-(CH_2)_3-$	464	465	Weak	13	1	170
2	$-(CH_2)_2CH(C_2H_5)-$	310	786	0.3	2	3	560
3	$-(CH_2)_2CH(n\text{-}C_3H_7)-$	152	671	0.5	1	3	150
4	$-(CH_2)_4-$	300	88	0.2	4	3	70
5	$-(CH_2)_3CH(CH_3)-$	408	265	Weak	10	2.5	120
6	$-(CH_2)_3CH(C_2H_5)-$	561	1754	Weak	2	10	130
7	$-(CH_2)_3CH(n\text{-}C_3H_7)$	213	376	Weak	6	2.5	170
8	$-(CH_2)_3CH(i\text{-}C_3H_7)-$	268	604	Weak	10	10	180
9		260	182	Weak	30	1.5	
	$C_6H_5(CH_2)_2YOCOC_6H_2(OCH_3)_3$-3,4,5						
10		157	103	0.8	6	0.5	50
11		229	169	0.5	10	0.5	300
12		300	165	1.0	13	2	150
	$C_6H_5(CH_2)_2N(C_2H_5)YOCOR$						
	Y / R						
13	$-(CH_2)_4-$ / $3,4\text{-}(CH_3O)_2C_6H_3-$	213	± (the depressor action is preceded by a pressor action)	0.5	6	1	175
14	$-(CH_2)_2CH(C_2H_5)-$ / $4\text{-}NH_2C_6H_4-$	351	253	Weak	1	3	55
	$RR_1N(CH_2)_4OCOC_6H_2(OCH_3)_3$-3,4,5						
	R / R_1						
15	$C_6H_5(CH_2)_2-$ / $-n\text{-}C_3H_7$	189	73	0.3	20	2	120
16	$4\text{-}HOC_6H_4(CH_2)_2-$ / $-n\text{-}C_3H_7$	201		0.3	13	2	
17	$C_6H_5CHOHCH(CH_3)-$ / $-n\text{-}C_3H_7$	224	86	Weak	30	4	75
18	$4\text{-}HOC_6H_4CH_2CH(CH_3)-$ / $-n\text{-}C_3H_7$	1283	340	1	50	1.5	110
19	$4\text{-}HOC_6H_4CH_2CH(CH_3)-$ / $-n\text{-}C_4H_9$	565	399	0.5	4	2.5	90
20	$2\text{-}CH_3OC_6H_4CH_2CH(CH_3)-$ / $-C_2H_5$	150	147	Weak	95	3.5	60
21	$3,4\text{-}(HO)_2C_6H_3CH_2CH(CH_3)-$ / $-n\text{-}C_3H_7$	231	1044	Weak	2	0.5	120
22	$4\text{-}HOC_6H_4CHOHCH(CH_3)-$ / $-n\text{-}C_3H_7$	223	105	Weak	50	5	30
23	$C_6H_5(CH_2)_3-$ / $-C_2H_5$	226	28	0.3	6	2.5	95
	$RR_1N(CH_2)_5OCOC_6H_2(OCH_3)_3$-3,4,5						
	R / R_1						
24	$2\text{-}CH_3OC_6H_4(CH_2)_2-$ / $-C_2H_5$	535	356	0.4	2	2	110
25	$4\text{-}HOC_6H_4CH_2CH(CH_3)-$ / $-n\text{-}C_3H_7$	215	117	0.8	10	4	180
26	$2\text{-}CH_3OC_6H_4CH_2CH(CH_3)-$ / $-C_2H_5$	221	24	0.2	10	1.5	75

isopropylamines). We also altered the alkylene chains between the nitrogen and the oxygen atom, introduced other substituents at the nitrogen atom and replaced the trimethoxybenzoic acid by other acids. The structures of the compounds are listed in Tables I–III. The compounds were investigated with regard to several pharmacological properties, since it was uncertain whether the properties of reserpine would still be found in these structures. Furthermore, phenethylamine derivatives with some structural analogy to reserpine might also show other interesting pharmacological properties.

Methods

Estimation of the A.D.C.[3] on the Blood Pressure of Rats.—Glaxorats (180–240 g. ♂ and ♀) were anesthetized with urethane. The blood pressure was measured from the carotid artery by means of a mercury manometer. Each compound was tested in at least 3 doses (dose increment 2). The lowest dose had to cause a lowering of the blood pressure by 15–20 mm. The animals were used for one compound only. The blood pressure lowering activity is expressed as the A.D.C., *i.e.*, the product of the maximum lowering of the blood pressure (in mm.) and the time interval of the depression (in min.) divided by twice the dose (in mg./kg.). The A.D.C. values for each dose were estimated in at least 3 animals. In the tables the arithmetical means are given.

Antispasmodic Activity *in vitro*.—The *in vitro* spasmolytic activity was determined according to the method of Magnus.[4] Segments of 2–3 cm. length of the ileum of the guinea pig (250–450 g.) were suspended in oxygenated Tyrode solution at 37°. Submaximum contractions with $BaCl_2$ and with carbamylcholine were evoked every 3 min. The drug was added to the bath 30 sec. before the addition of the spasmogen. Determination of the activity was carried out by comparing the reduction of the spasmogenic contraction caused by 2 doses of the compound in question with the effects caused by papaverine. The relative activities stated are the mean values of at least two separate determinations.

Adrenolytic Activity.—The *in vitro* adrenolytic activity was determined in isolated strips of the spleen. These were suspended

(3) A.D.C. is the Activity Dose Coefficient.

(4) R. Magnus, *Pflügers Arch. ges. Physiol.*, **102**, 123 (1904); **103**, 515 (1904).

TABLE II

ACTIVE SPASMOLYTICS

	Compounds $RC_6H_4CH_2CH(CH_3)N(C_2H_5)YOCOR_1$			A.D.C.[a]	Guinea pig ileum		Rabbit ileum		*In vivo*	LD_{50}
	R	Y	R_1	(rat)	Carbamylcholine (Pap. = 1)	$BaCl_2$ (Pap. = 1)	Carbamylcholine (Pap. = 1)	$BaCl_2$ (Pap. = 1)	cardiospasms (Pap. = 1)	i.p. mg./kg. (mice)
27	4-HO–	$-(CH_2)_4-$	3,4,5-$(CH_3O)_3C_6H_2-$	116	50	2.5				75
28	4-CH_3O–	$-(CH_2)_4-$	3,4,5-$(CH_3O)_3C_6H_2-$	14	125	4	5	3.0	2	160
29	3-CH_3O–	$-(CH_2)_4-$	3,4,5-$(CH_3O)_3C_6H_2-$	61	95	7	4	4.0	1	150
30	2-CH_3O–	$-(CH_2)_4-$	3,4,5-$(CH_3O)_3C_6H_2-$	150	95	3.5	2	2.0		60
31	4-C_2H_5O–	$-(CH_2)_4-$	3,4,5-$(CH_3O)_3C_6H_2-$	36	125	4	12	1.8		220
32	4-CH_3O–	$-(CH_2)_5-$	3,4,5-$(CH_3O)_3C_6H_2-$	47	250	8	3	2.6	1	130
33	2-CH_3O–	$-(CH_2)_5-$	3,4,5-$(CH_3O)_3C_6H_2-$	98	95	2.5	2	3.8	2	110
34	4-CH_3O–	$-(CH_2)_6-$	3,4,5-$(CH_3O)_3C_6H_2-$	30	150 (0.1 × atropine)	4	8	2.5	1	150
35	3,4-$(CH_3O)_2$	$-(CH_2)_6-$	3,4,5-$(CH_3O)_3C_6H_2-$	41	75	4	22	3.0		150
36	4-CH_3O–	$-(CH_2)_4-$	3,4-$(CH_3O)_2C_6H_3-$	52	125	4	21	2.5	3	150
37	3-CH_3O–	$-(CH_2)_4-$	3,4-$(CH_3O)_2C_6H_3-$	80	190	10	4	3.4		180
38	3,4-$(CH_3O)_2$	$-(CH_2)_4-$	3,4-$(CH_3O)_2C_6H_3-$	31	100	3				200
39	4-CH_3O–	$-(CH_2)_6-$	3,4-$(CH_3O)_2C_6H_3-$	24	125	4	24	2.0	3	200
40	4-CH_3O–	$-(CH_2)_4-$	4-$CH_3OC_6H_4-$	54	125	3	2	1.3		180
41	3,4-$(CH_3O)_2$	$-(CH_2)_4-$	3,4,5-$(C_2H_5O)_3C_6H_2-$	30	75	3.5				250
	4-$RC_6H_4CHR_1CH(CH_3)$-$N(n\text{-}C_3H_7)(CH_2)_4OCOC_6H_2(OCH_3)_3$-3,4,5									
	R		R_1							
42	CH_3O–		H	14	125	4	5.5	1.7	2	215
43	HO–		H	1283	50	1.5				110
44	HO–		HO–	223	50	5				30
45	4-$C_2H_5OCOC_6H_4(CH_2)_2N(C_2H_5)(CH_2)_4OCOC_6H_2$-$(OCH_3)_3$-3,4,5			86	55	2	3.1	<1.0		70
46	$C_6H_5(CH_2)_2N(CH_3)(CH_2)_4OCOC_6H_2(OCH_3)_3$-3,4,5			105	55	2	3.7	3.0		55
47	4-$CH_3OC_6H_4CH_2C(CH_3)_2N(C_2H_5)(CH_2)_4OCOC_6H_2$-$(OCH_3)_3$-3,4,5			59	65	3	1.0	<1.0		180

in oxygenated Ringer solution containing epinephrine tartrate (2.5 γ of epinephrine ml.). The drug was brought into contact with this preparation for 20 min. The relative activity was calculated from the relaxation caused by the test compound compared with the effect of a chosen standard compound (Table III, no. 53). This standard possessed 5% of the activity of dihydroergotamine tartrate.

I.P. Toxicity by Way of a Two-Point Test.—The toxicity upon i.p. administration was determined in albino mice (♂ and ♀, weight 18–22 g.). Of each compound two doses were tested in 10 mice. The lowest dose caused a mortality of less than 50%, the highest a mortality of more than 50%. The LD_{50} was determined graphically.

Spasmolytic Activity in the Isolated Ileum of the Rabbit.—The *in vitro* spasmolytic activity on the ileum of the rabbit was determined in the intestine, which was kept in a state of constant contraction by means of a spasmogen. To this end, segments of the ileum of the rabbit were suspended in an oxygenated Tyrode solution at a temperature of 37°, which solution contained 1% of $BaCl_2$ or 0.001% of carbamylcholine chloride, respectively. The spasmolytic activity against papaverine was established in a Latin square, using always 4 ileum segments of the same experimental animal. From these data the relative activity was determined graphically.

Spasmolytic Activity on the Cardia on the Vagotomized Rabbit.—This determination was carried out according to the method of Brücke and Stern.[5] Papaverine was used for comparison. The relative activity was determined as a means from the results obtained in at least 3 rabbits.

Results

The compounds listed have several interesting properties, especially as depressants, antispasmodics, and adrenolytics. A number of compounds also have bronchodilator activity. These activities as well as the LD_{50} i.p. in mice, are summarized in Tables I–III. Table I lists the more active depressants (A.D.C. above 150). These substances also were tested on anaesthetized cats. The more active spasmolytics (neurotropic above 50× and musculotropic above 1× papaverine) have been summarized in Table II. They were also tested on the isolated rabbit ileum; several of these compounds were examined *in vivo* by the cardiospasm method. The low adrenolytic activities of these compounds are not reported.

The compounds in Table I and II are divided in subgroups, which differ in one or two chemical respects only. This facilitates comparison of compounds for structure-activity relationships. In Table III a number of compounds is brought together, which may illustrate our remarks on structure-activity relationship.

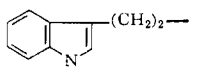
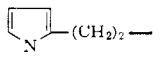
Discussion

Concerning the depressant activity, several conclusions may be drawn regarding the chemical structure of these compounds. From Table I it is apparent that the more active blood pressure-lowering substances are tertiary phenethylamine and β-hydroxyphenylisopropylamine derivatives. The substituents at the amino-group preferably should be an ethyl or propyl group (compare compounds 4, 5, and 22 with 53–56) and an alkanol group esterified with an alkoxybenzoic acid. A combination of particular structural features is apparently favorable for depressant activity. Departure from the phenethylamine structure leads to clearly diminished activity (compare compound 4 with compounds 23 and 48–52) just like substitution with alkoxyl groups other than by *o*-methoxy (Table II).

(5) F. T Brücke and P. Stern, *Arch. exp. Path. Pharmakol.*, **189**, 311 (1938).

TABLE III

MISCELLANEOUS COMPOUNDS

	Compounds $R_1R_2N(CH_2)_4OCOC_6H_2(OCH_3)_3$-3,4,5			Antispasmodic act. guinea pig ileum			
	R_1	R_2	A.D.(.3 rat	Carbamylcholine (Papaverine = 1)	$BaCl_2$ (Pap. = 1)	Adrenolytic activity (cpd. 53 = 1)	LD_{50} i.p. mg./kg. (mice)
48	$-C_2H_5$	$-C_2H_5$	13	1	<0.5	Weak	180
49	$C_6H_5CH_2-$	$-C_2H_5$	63	6	1	Weak	190
50	$C_6H_5CH_2CH(CH_3)-$	$-C_2H_5$	15	4	2.5	Weak	220
51		$-C_2H_5$	41	9	3.5	0.6	130
52		$-C_2H_5$	93	1	1	Weak	280
53	$C_6H_5(CH_2)_2-$	H–	120	<1	1.5	1	120
54	$C_6H_5(CH_2)_2-$	$-CH_3$	105	55	2	1.7	55
55	$C_6H_5(CH_2)_2-$	$C_6H_5CH_2$	19	3	<0.5	Weak	580
56	$4\text{-}HOC_6H_4CHOHCH(CH_3)-$	H–	41	<1	0.5	0.2	70
57	$C_6H_5(CH_2)_2N(C_2H_5)(CH_2)_2OCOC_6H_2(OCH_3)_3$-3,4,5		109	1	0 5	Weak	340
58	$C_6H_5(CH_2)_2N(C_2H_5)(CH_2)_6OCOC_6H_2(OCH_3)_3$-3,4,5		31	30	4	0.2	
	$C_6H_5(CH_2)_2N(C_2H_5)(CH_2)_4OR$ R						
59	H–		19			Weak	170
60	$C_6H_5CH_2-$		30	7	1	Weak	70
61	CH_3CO-		94	<1	<0.5	Weak	220
62	$C_2H_5CH(CH_3)CO-$		29	4	<0.5	Weak	170
63	C_6H_5CO-		60	10	2	Weak	300
64	$4\text{-}NH_2C_6H_4CO-$		37	4	1	0.5	100
65	$4\text{-}(CH_3)_2NC_6H_4CO-$		53	13	<1	0.7	190
66	$3,5\text{-}(NH_2)_2C_6H_3CO$		31	<1	0.5	Weak	280
67	$4\text{-}CH_3OC_6H_4CH_2CH(CH_3)N(C_2H_5)(CH_2)_4OH$		15	3	<0.5	Weak	120
68	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH(CH_3)N(C_2H_5)$-$(CH_2)_4OCOC_6H_2(OCH_3)_3$-3,4,5		40	5	0.5	Weak	130
69	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH(CH_3)N(C_2H_5)$-$(CH_2)_4OCOC_6H_4OCH_3$-4		40	6	2		
70	$4\text{-}CH_3OC_6H_4CH_2CH(CH_3)N(C_2H_5)(CH_2)_3$-$OCOC_7H_2(OCH_3)_3$-3,4,5		49	15	2	Weak	170
71	$4\text{-}CH_3OC_6H_4CH_2CH(CH_3)N(C_2H_5)(CH_2)_4$-$OCOCH(C_6H_5)_2$		<10	40	1	Weak	280

Also the distance between the amino and hydroxyl group is important. For distances of two or six methylene groups, depressant activity diminishes markedly (compare compounds 1 and 4 with compounds 57 and 58). The compounds which are not alkoxybenzoate esters have as a rule a decreased activity (compare compounds 4 and 13 with compounds 59–66). Perhaps the *p*-aminobenzoate is an exception to this rule (compound 14).

The musculotropic spasmolytic activity, measured against barium chloride, is larger for most of the compounds than that of papaverine; some of the important exceptions are the dialkylamino compound 48, the nonesterified amino alcohol 67 and those esterified by alkanecarboxylic acids (61, 62) with activities less than 0.5 × papaverine. With regard to the spasmolytic activities against carbamylcholine, a relatively low neurotropic spasmolytic activity is observed when the aralkyl group is not substituted (Table I). Substitution of two hydroxyl (21) or three alkoxyl groups (68, 69) leads to diminished activity compared with the compounds substituted with one hydroxyl or one or two methoxy groups. Especially tertiary β-alkoxyphenylisopropylamine derivatives are active antispasmodics (Table II). The substituents at the amino group should be an ethyl or propyl group (compare compounds 53, 56, and 19 with 4, 22, and 18 respectively) and a hydroxyalkyl group of at least four carbon atoms (compare compound 70 with compounds 28, 32, and 34) esterified by an alkoxybenzoic acid. The influence of the acyl group is not always very specific (compare compounds 4 and 13 with compounds 60–66), though it is clear that the free amino alcohol has little activity (67), whereas the mono-, di- or trimethoxybenzoates are more active than the diphenylacetate (compare compound 71 with compounds 28, 36, and 40). On the whole it may be said that these compounds form a new class with spasmolytic activity of musculotropic as well as of neurotropic origin. The musculotropic action is of a higher order (often 2–5 × that of papaverine) than that generally found in esters of amino alcohols. The relationship between structure and activity is different from the normal relationship present in aminoalkyl esters. Thus the dialkylaminobenzoates have little activity. Substitution of one alkyl group by an aralkyl group causes an increase of both the musculotropic and the neutrotropic activity. Comparison of the N-ethylphenethylaminoethyl ester of diphenyl-

acetic acid with the diethylaminoethyl ester of this acid showed that the aralkylamino compound had a considerably reduced neurotropic activity. Other deviations are the length of the alkylene chain (here preferably more than three carbon atoms; in the substituted phenylacetic acid series preferably two or three carbon atoms) and the other acids which give high activity. The 3,4,5-trimethoxybenzoate of β-diethylaminoethanol is, for instance, much less active than the corresponding diphenylacetate ester.

The phenethylamine derivatives with a small substituent, *e.g.*, a hydrogen atom or a methyl group at the nitrogen atom (53, 54) possess considerable adrenolytic activity. Especially piperidine (10–12) and *p*-hydroxyphenylisopropylamine derivatives (18, 19, and 25) are fairly active.

Potent Decarboxylase Inhibitors. Analogs of Methyldopa [1]

M. SLETZINGER, J. M. CHEMERDA, AND F. W. BOLLINGER

Merck Sharp and Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N. J.

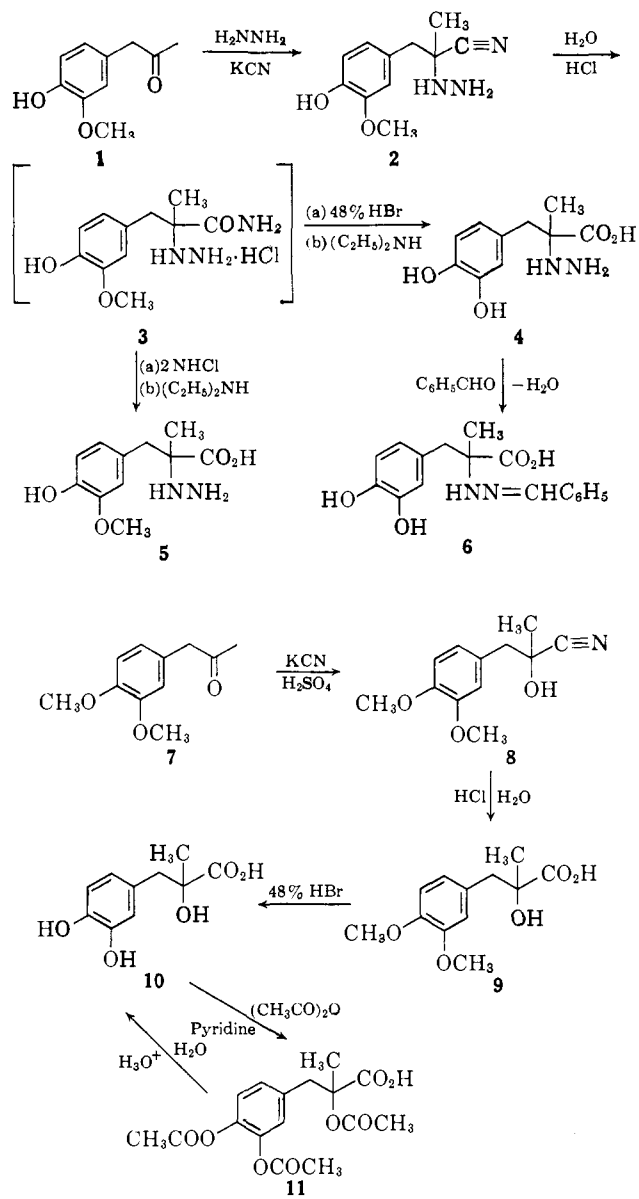
Received June 11, 1962

Two new classes of compounds analogous to L-α-methyl-3,4-dihydroxyphenylalanine, formed by replacing the α-amino group with α-hydroxy and α-hydrazino groups, have been prepared. Comparison with the parent compound in the ability to inhibit mammalian DOPA-decarboxylase shows that both new classes are potent inhibitors. Of the compounds prepared DL-α-hydrazino-α-(3,4-dihydroxybenzyl)propionic acid exhibits a potency *in vitro* approximately one thousand times that of the parent compound.

In a search for hypotensive compounds related to L-α-methyl-3,4-dihydroxyphenylalanine, two new classes of compounds were prepared. The new analogs can be pictured by substituting α-hydrazino or α-hydroxyl groups for the α-amino group of the parent compound. These compounds were used to test the hypothesis that hypotensive action is paralleled by ability to inhibit mammalian decarboxylase. The synthesis of the α-hydrazino analog began with a Strecker reaction in which 1-(4′-hydroxy-3′-methoxyphenyl)-2-propanone (**1**) was treated with aqueous hydrazine and potassium cyanide. This condensation, though reversible, succeeds because product (**2**) is sparingly soluble in the solvent. In hot chloroform the hydrazino nitrile (**2**) reverts to starting materials.

Hydrolysis of the hydrazino nitrile (**2**) is accomplished in two stages. The nitrile moiety is hydrolyzed to an amide by fortified hydrochloric acid at −10 to 0°. Efforts to crystallize the amide (**3**) as the hydrochloride salt or free base did not succeed. The amide (**3**) was converted to the desired hydrazino acid (**4**) by refluxing with constant boiling hydrobromic acid. Other methods of hydrolysis were tried but none proved to be as good. Substitution of dilute hydrochloric acid for constant boiling hydrobromic acid permitted isolation of the analogous 3-methoxylated acid (**5**). DL-α-Hydrazino-α-(3,4-dihydroxybenzyl)propionic acid (**4**) was characterized as its benzaldehyde derivative (**6**).

The synthesis of the second class of analogs proceeds from 1-(3′,4′-dimethoxyphenyl)-2-propanone (**7**) which by the method of Davies, *et al.*,[2] is converted to 2-(3′,4′-dimethoxybenzyl)lactonitrile (**8**). Hydrolysis of the cyanohydrin (**8**) to the α-hydroxy acid (**9**) with refluxing constant boiling hydrochloric acid at atmospheric pressure for 5 hours cleaved the methoxyl groups to some extent. The methoxyl group of 3-methoxytyramine is cleaved about 90% by hydrolysis



(1) ALDOMET®.

(2) A. G. Davies, F. M. Ebeid, and J. Kenyon, *J. Chem. Soc.*, 3154, (1957).