TABLE II

Sex	Weight, kg.	Test material	Amount introduced into stomach, ml.	Amount drained from stomach, ml.	Mucosa present in stomach fluid	Gross appearance of gastric mucosa
Male	20	1,2,2-Trichloro-1,1,2-trifluoroethane[a]	200	200	...	Normal
Female	24	Same	200	200	...	Normal
Male	24	Ethyl alcohol	135	180	+	Deep red in color; swollen; leathery to touch
Female	16	Same	200	270	+	Deep red in color; swollen; leathery to touch
Female	20	None	None	None	...	Normal

[a] Mol. wt. 187.4, b.p. 47.6°, *d* (liquid at b.p.) 1.510 g./ml., solubility, 0.009% in H_2O at 21.2°.

Histological examination of the biopsy specimens indicated that no significant histological change occurred in the 1,2,2-trichloro-1,1,2-trifluoroethane-treated stomachs while marked hyperemia and edema with minimal inflammation was found in the alcohol-treated stomachs as compared to the control specimen.

Analogs of Methyldopa and Dopa. Hydantoic Acids and Hydantoins

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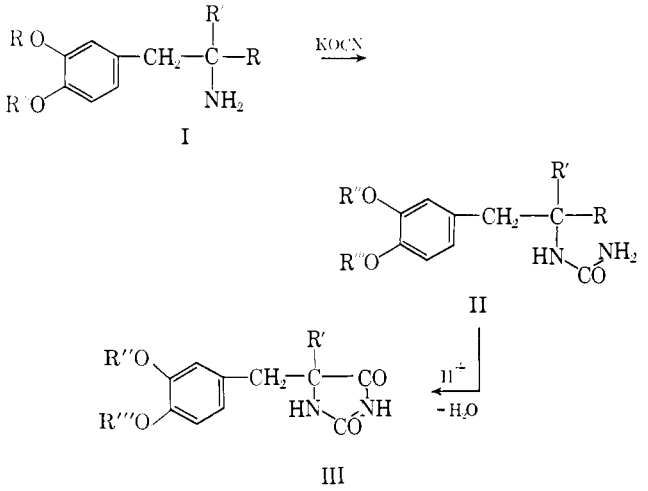
As part of a program to discover hypotensive compounds related to methyldopa (Ia), two new classes of compounds were prepared. The new analogs were 4-(3,4-dihydroxybenzyl)-4-methylhydantoic acid (IIa) and α-(4-hydroxy-3-methoxybenzyl)-α-ureidopropionitrile (IId). It had already been shown that the ability to inhibit mammalian decarboxylase was not a necessary corollary for hypotensive activity.[2,3] Thus, these analogs were not tested *in vitro* but were tested *in vivo* for their ability to depress the blood pressure of hypertensive or normotensive rats. Neither compound, however, when tested at dose levels of 100 mg./kg., i.p., showed any activity, while α-methyldopa was active in doses of 20–40 mg./kg., i.p.

Since conditions which permitted the hydrolysis of the extremely stable hydantoin led to rapid hydrolysis of the intermediate hydantoic acid to the amino acid, the desired hydantoic acids were prepared by the classical method of Dakin[4] from the amino acid. On refluxing the amino acid with potassium cyanate in aqueous solution, the salt of the hydantoic acid was obtained. The hydantoic acids were isolated after acidification with hydrochloric acid and extraction with ethyl acetate. In this manner, L(−)- and D(+)-4-(3,4-dihydroxybenzyl)-4-methylhydantoic acid (IIa) were prepared from methyldopa (Ia), L(+)-4-(3,4-dihydroxybenzyl)hydantoic acid (IIb) from dopa (Ib), and DL-4-(4-hydroxy-3-methoxybenzyl)-4-methylhydantoic acid (IIc) from the racemic 3-methoxy analog of methyldopa (Ic). DL-α-(4-hydroxy-3-methoxybenzyl)-α-ureidopropionitrile (IId) was prepared by treatment of DL-α-amino-α-(4-hydroxy-3-methoxybenzyl)propionitrile with potassium cyanate under the conditions of Herbst and Johnson.[5]

The hydantoic acids and α-ureido nitrile were readily converted into the corresponding hydantoins by refluxing in 6 *N* mineral acid. Thus, the following hydantoins were prepared: L(−)- and D(+)-5-(3,4-dihydroxybenzyl)-5-methylhydantoin (IIIa) from IIa, L(−)-5-(3,4-dihydroxybenzyl)hydantoin (IIIb) from IIb, and DL-5-(4-hydroxy-3-methoxybenzyl)-5-methylhydantoin (IIIc) from either IIc or IId.



I

II

III

I and II

a, R = COOH, R′ = CH_3, R″ = R‴ = H
b, R = COOH, R′ = R″ = R‴ = H
c, R = COOH, R′ = R″ = CH_3, R‴ = H
d, R = CN, R′ = R″ = CH_3, R‴ = H

III

a, R′ = CH_3, R″ = R‴ = H
b, R′ = R″ = R‴ = H
c, R′ = R″ = CH_3, R‴ = H

As might be expected, hydantoin formation in the methyldopa series is not accompanied by racemization, even after refluxing in 6 *N* HCl for up to 6 hr., while in the dopa series, an optically inactive product was obtained after similar treatment. Refluxing in

(1) ALDOMET®.

(2) M. Sletzinger, J. M. Chemerda, and F. W. Bollinger, *J. Med. Chem.*, **6**, 101 (1963).

(3) L. Gillespie, Jr., J. A. Oates, J. R. Crout, and A. Sjoerdsma, *Circulation*, **25**, 281 (1962).

(4) H. D. Dakin, *Am. Chem. J.*, **44**, 48 (1910); *J. Biol. Chem.*, **8**, 25 (1910–1911).

(5) R. M. Herbst and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 2463 (1932).

TABLE I

ACID-CATALYZED RACEMIZATION

Time, min.	Hydantoins, $[\alpha]^{25}D$, deg. (c 1, H_2O) (IIIa) L(−)-Methyldopa	(IIIb) L(−)-Dopa
15	−52.1	−102.0
60	−51.0	−24.5
120	−52.0	−14.2
360	−51.3	0.0

acid for only 15 min. gave a product having $[\alpha]^{25}D$ −102.0° (*c* 1, H_2O) for the dopa derivative; however, this value must be taken as a minimum because of the racemization which takes place as in Table I. The specific rotations of the amino acid, hydantoic acid, and hydantoin of L(−)- and D(+)-methyldopa and L(−)-dopa are summarized in Table II. The reactions, isolations, and purifications were followed by paper chromatography and are reported in Table III.

TABLE II

SPECIFIC ROTATION DATA OF DOPA AND METHYLDOPA ANALOGS

	$[\alpha]^{25}D$, deg. (c 1) R′ = H (levo)	R′ = CH_3 (levo)	R′ = CH_3 (dextro)
Amino acid	(Ib) −12.7, 4% HCl	(Ia) −2.0, 4% HCl	(Ia) +2.0, 4% HCl
Hydantoic acid	(IIb) +23.6, H_2O, pH 2.5	(IIa) −58.6, H_2O, pH 2.5	(IIa) +58.0, H_2O, pH 2.5
Hydantoin	(IIIb) −102.0, H_2O, pH 5.4	(IIIa) −50.3, H_2O, pH 5.4	(IIIa) +51.3, H_2O, pH 5.4

Experimental

Infrared spectra were used in the characterization of all compounds reported. Rotations were determined in a Zeiss precision photoelectric polarimeter, using a 0.5 dm. cell. All melting points were measured on samples in open capillaries with total immersion thermometers and are corrected. Resolved methyldopa was supplied by Dr. E. W. Tristram and the aminonitrile by Dr. D. F. Reinhold, both from these laboratories. Dopa was obtained from commercial sources.

L(−)- and D(+)-4-(3,4-Dihydroxybenzyl)-4-methylhydantoic Acid (IIa).—To 5.0 g. (0.024 mole) of L(−)-α-methyl-3,4-dihydroxyphenylalanine (methyldopa) (Ia) in 25 ml. of boiling water, in a nitrogen atmosphere,[6] 9.0 g. (0.111 mole) of potassium cyanate was added. The temperature was lowered to 60° and maintained for 3 hr. The reaction mixture was cooled in an ice bath, acidified with concentrated hydrochloric acid to pH 2.5, and extracted exhaustively with ethyl acetate. The extracts were dried over sodium sulfate and concentrated to about 25 ml. On standing overnight at 4°, a glass-like precipitate was obtained. The product, when filtered, washed with ethyl acetate, and dried *in vacuo* at 25° overnight, weighed 3.82 g. (63.6%); m.p. 168–169° (effervescence). The product was recrystallized from a minimum amount of boiling water and obtained as white needles which, after drying at 60° *in vacuo*, had m.p. 170–171° (effervescence), $[\alpha]^{25}D$ −58.6° (*c* 1, H_2O, pH 2.5).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 52.00; H, 5.51; N, 11.02. Found: C, 52.04; H, 5.48; N, 10.92.

The corresponding D(+)-isomer (IIa) was also prepared, m.p. 169–171° (effervescence), $[\alpha]^{25}D$ +58.0° (*c*, 1, H_2O, pH 2.5).

Found: C, 52.30; H, 5.33; N, 11.11.

L(+)-4-(3,4-Dihydroxybenzyl)hydantoic Acid (IIb).—This compound was prepared from L(−)-3,4-dihydroxyphenylalanine (dopa) (Ib) using the same procedure as described for IIa. The isolated product, 2.05 g. (82%), was recrystallized from boiling water, and dried at 60° *in vacuo*, m.p. 105.5° (effervescence), $[\alpha]^{25}D$ +23.56° (*c* 1, H_2O, pH 2.5).

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.00; N, 11.65. Found: C, 49.91; H, 5.05; N, 11.42.

DL-4-(4-Hydroxy-3-methoxybenzyl)-4-methylhydantoic Acid (IIc).—This compound was prepared from DL-α-methyl-3-methoxy-4-hydroxyphenylalanine (Ic) using the same procedure as described for IIa. The isolated product, 2.1 g. (62.5%), was recrystallized from boiling water, and dried at 60° *in vacuo*, m.p. 172–173° (effervescence).

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.80; H, 5.96; N, 10.45. Found: C, 54.04; H, 5.96; N, 10.60.

DL-α-(4-Hydroxy-3-methoxybenzyl)-α-ureidopropionitrile (IId).—To 5.0 g. (0.024 mole) of DL-α-amino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (Id) in 30 ml. of 50% acetic acid was added 4.0 g. (0.050 mole) of potassium cyanate. The solution was heated at 80–90° for 1 hr., then cooled to room temperature, and concentrated ammonium hydroxide added to pH 7.0. The solution was poured into 150 ml. of cold water and aged overnight at 4°. The product, when filtered, washed with cold water, and dried *in vacuo* at 60° overnight, yielded 3.38 g. (55.8%). Recrystallization from hot 50% aqueous methanol followed by drying *in vacuo* at 60° gave 2.65 g., m.p. 188–189°.

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 57.80; H, 6.03; N, 16.90. Found: C, 57.10; H, 6.08; N, 16.35.

L(−)- and D(+)-5-(3,4-Dihydroxybenzyl)-5-methylhydantoin (IIIa).—Two grams (0.008 mole) of L(−)-4-(3,4-dihydroxybenzyl)-4-methylhydantoic acid (IIa) was refluxed in 6 *N* hydrochloric acid for 1 hr. The reaction mixture was cooled in an ice bath for 3 hr., the crystalline product filtered, and washed with cold water followed by acetone. After drying *in vacuo* at 60° overnight, the product, 1.5 g. (80.7%), had m.p. 235–236°, $[\alpha]^{25}D$ −50.3° (*c* 1, H_2O, pH 5.4).

TABLE III

PAPER CHROMATOGRAPHIC DATA ON DOPA AND METHYLDOPA ANALOGS[a]

Compound	R_f	Reagent A	B	C	D
Ia	0.48	Red	...	Blue	Purple
Ib	0.35	Red	...	Blue	Purple
Ic	0.55	...	...	Blue	Purple
Id	0.86	...	...	Blue	...
IIa	0.70	Red	Yellow	Blue	...
IIb	0.87	Red	Yellow	Blue	...
IIc	0.81	...	Yellow	Blue	...
IId	0.87	...	Red	Blue	...
IIIa	0.78	Red	...	Blue	...
IIIb	0.61	Red	...	Blue	...
IIIc	0.86	...	...	Blue	...

[a] The chromatograms were run in the descending fashion on Whatman No. 1 paper using as developer the upper phase of a system composed of butanol-acetic acid–water (4:1:5). The compounds were detected with the following reagents. A, **potassium ferricyanide** [James Ferricyanide Reagent, W. O. James, *Nature*, **161,** 851 (1948)]. This reagent gave bright red zones with 2,3- and 3,4-dihydroxy substituted phenyl compounds. After drying, the chromatograms were sprayed with a 0.44% aqueous solution (w./v.) followed by a 5% sodium carbonate solution and dried at room temperature. B, ***p*-dimethylaminobenzaldehyde** [Barrenscheen–Weltmann Reagent, H. K. Barrenscheen and O. Weltmann, *Biochem. Z.*, **131,** 591 (1922); D. M. Phillips, *Biochim. Biophys. Acta*, **13,** 560 (1954)]. This reagent gave bright yellow zones with hydantoic acids. After drying, the chromatograms were sprayed with a solution of 4% *p*-dimethylaminobenzaldehyde in 1 *N* HCl (w./v.) and dried at room temperature. C, **phosphomolybdic and phosphotungstic acids** [Folin–Denis Reagent, O. Folin and W. Denis, *J. Biol. Chem.*, **12,** 239 (1912)]. This reagent gave blue zones with monohydroxy substituted phenyl compounds. After drying the chromatograms were sprayed with a mixture composed of 10% sodium tungstate, 2% phosphomolybdic acid, and 10% phosphoric acid diluted with an equal volume of 30% NH_3 and 2 volumes of ethanol, and dried at room temperature. D, **ninhydrin.** This classical reagent gave purple zones with amino acids. After drying, the chromatograms were sprayed with a 0.25% (w./v.) solution in 95% ethanol, dried, and heated at 100° for 10 min.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 56.00; H, 5.08; N, 11.87. Found: C, 56.71; H, 4.94; N, 12.15.

The corresponding D(+)-isomer (IIIa) was also prepared, m.p. 236–237°, $[\alpha]^{25}D$ +51.3° (*c* 1, H_2O, pH 5.4).

Anal. Found: C, 56.72; H, 5.24; N, 11.72.

(6) The phenolic groups are rapidly oxidized at elevated temperature in a basic solution.

L(−)-**5-(3,4-Dihydroxybenzyl)hydantoin (IIIb).**[7]—A study of the acid-catalyzed racemization of L(+)-4-(3,4-dihydroxybenzyl)-hydantoic acid (IIIb) was made by refluxing 1-g. (0.005 mole) samples of IIb in 10 ml. of 6 *N* hydrochloric acid for various lengths of time. The hydrochloric acid was removed by repeated evaporation to dryness *in vacuo*. The products were then crystallized from hot water and isolated in about 70% yield. The samples were dried *in vacuo* at 40° overnight before analysis. The extent of racemization of these hydantoins derived from L(−)-dopa are compared to those derived from L(−)-methyldopa in Table II.

DL-**5-(4-Hydroxy-3-methoxybenzyl)-5-methylhydantoin (IIIc).**—This compound was prepared from DL-α-(4-hydroxy-3-methoxybenzyl)-α-ureidopropionitrile (IId) by the same procedure used for IIIa. The resulting product was isolated in 75.5% yield and had m.p. 233–235°.

Anal. Calcd.: C, 57.60; H, 5.60; N, 11.20. Found: C, 56.64; H, 5.30; N, 10.67.

This compound was also prepared from DL-4-(4-hydroxy-3-methoxybenzyl)-4-methylhydantoic acid by the same procedure. The physical characteristics were identical with IIIc.

Acknowledgment.—The authors are indebted to Mr. R. W. Walker for the infrared analyses, to Mr. R. N. Boos and his associates for microanalytical data, and to Dr. C. A. Stone, Dr. L. S. Watson, Dr. C. C. Porter, and Dr. R. W. Schayer of the Merck Institute for Therapeutic Research for the biological testing of these compounds.

(7) M. Damodaran and R. Ramaswamy, *Biochem. J.*, **31**, 2149 (1937), reported the preparation of this compound, m.p. 212°.

Some Catalytic Hydrogenations in the Presence of Aryl Chloride

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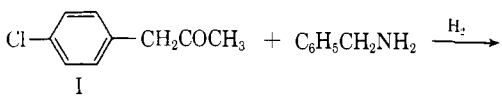
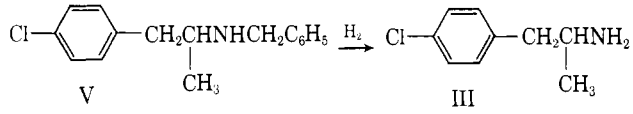
There was a need in this laboratory for 2-amino-1-(4-chlorophenyl)propane (III) in an appetite-depressant program. The preparation of this compound by catalytic reduction instead of the described method[1] would give us an opportunity to study hydrogenation in the presence of aryl chloride. Previously, in a reduction of —N=CH— function in the presence of aromatic halogen,[2] we commented that too little work had been done on selective conversion of groups which gave amines of varying degrees of basicity, in the presence of aromatic halogen.

Reductive amination of 1-(4-chlorophenyl)-2-propanone (I) according to the method of Alexander and Misegades[3] failed. High pressure hydrogenation in the presence of Raney nickel gave only a small amount of III.

It seemed to be more advantageous to employ the following scheme.



I



V III

Following this series of reactions would give us an opportunity to evaluate the anorectic effect of a new compound (V). At the same time, we could study reductive alkylation in the presence of aromatic halogen, and perhaps of greater importance, to determine whether selective debenzylation could take place. Using commercially available platinum on carbon catalyst, V was obtained in fairly good yield without much accompanying side reaction, although hydrogenolysis of the chlorine atom can occur with the formation of 2-(N-benzylamino)-1-phenylpropane (IV) (see Experimental).

There is a recognized danger in the use of palladium on carbon for the conversion of V to III. It is not only the most efficient catalyst for the debenzylation of secondary and tertiary amines, but it is also the one of choice for dehalogenation. However, it was thought that dehalogenation could be suppressed by carrying out the reduction in the presence of an excess of acid.[2,4] Unfortunately, IV was the main product of reaction. Other catalysts were not able to bring about the desired results (see Table I). Hydrogenation in the presence of rhodium on carbon and also platinum resulted in the formation of another compound whose constitution is unknown and is being investigated further.

Experimental[5]

2-Amino-1-(4-chlorophenyl)propane (III).—Reductive amination of 1-(4-chlorophenyl)-2-propanone (I) was attempted in ethyl alcohol containing excess ammonia and ammonium chloride in the presence of prereduced platinum catalyst.[3] No uptake of hydrogen took place.

To a solution of 50.8 g. (0.3 mole) of I in 50 ml. of ethyl alcohol was added 10 g. of Raney nickel. The mixture was cooled to about −20° and 50 ml. of liquid ammonia was added. After warming to room temperature, the reaction mixture was hydrogenated under 103.33 kg./cm.^{2} pressure. Uptake of hydrogen appeared to be complete in about 5 hr. After removal of the material from the catalyst, the solution and washings were concentrated to dryness. The residue was treated with 0.3 mole of alcoholic hydrogen chloride and evaporated to dryness. The residue was treated with anhydrous ether. A solid was obtained. It was filtered and washed with ether. The hydrochloride salt weighed 6.2 g. (10% yield) and melted at 164° (lit.[1] m.p. 164–165°).

The nonbasic material recovered from the filtrate was not investigated except to note that it contained a hydroxyl group as seen from its infrared spectrum.

2-(N-Benzylamino)-1-(4-chlorophenyl)propane (V).—1-(4-Chlorophenyl)-2-propanone (42.0 g., 0.5 mole) and 26.8 g. (0.5 mole) of benzylamine were dissolved in 150 ml. of absolute ethyl alcohol. The solution was hydrogenated in the presence of 3.6 g. of 5% platinum on carbon[6] under 2–3 kg./cm.^{2} pressure. When uptake of hydrogen for 0.25 mole was complete (1 hr.), the solution was filtered from the catalyst and concentrated under reduced pressure. The residue was fractionated and the portion distilling at 159–164° (2.5 mm.), n^{25}D 1.5632, was collected; yield, 78%. In other runs the product distilled at 160–163° (3.0 mm.) and 171–175° (4–5 mm.), n^{25}D 1.5630–1.5632. Vapor phase chromatography showed that the distilled material was

(1) T. M. Patrick, Jr., E. T. McBee, and H. B. Haas, *J. Am. Chem. Soc.*, **68**, 1009 (1946).

(2) M. Freifelder, W. B. Martin, G. R. Stone, and E. I. Coffin, *J. Org. Chem.*, **26**, 383 (1961).

(3) E. R. Alexander and A. L. Misegades, *J. Am. Chem. Soc.*, **70**, 1315 (1948).

(4) R. Baltzly and A. P. Phillips, *ibid.*, **68**, 261 (1946).

(5) All melting points, taken on a Thomas-Hoover capillary apparatus, are corrected.

(6) Available from Baker & Company, Division of Engelhard Industries, Newark, N. J.