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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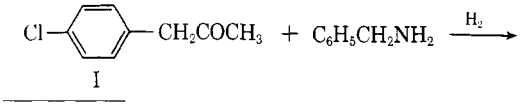
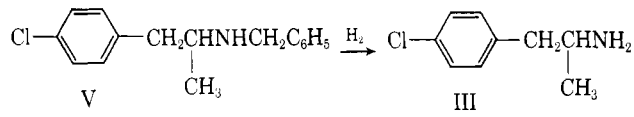
There was a need in this laboratory for 2-amino-1-(4-chlorophenyl)propane (III) in an appetite-depressant program. The preparation of this compound by catalytic reduction instead of the described method[1] would give us an opportunity to study hydrogenation in the presence of aryl chloride. Previously, 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.





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.

TABLE I

Method	Catalyst	% composition[h] I	III	IV	V
A	*a*	7.05	1.76	85.44	5.73
B	*a*	9.34	4.61	76.69	9.34
B	*b*	1.0	7.64	2.19[i]	67.96
B	*c*	<1.0	7.1	<3.0[j]	35.2
B	*d*, *e*			*k*	>90.
	f	±1.0	4.68	2.67[l]	67.52
B	*g*				

[a] 5% palladium on carbon. [b] 5% rhodium on carbon (2.6 g./0.1 mole of V). [c] 5% rhodium on carbon (2.6 g./0.05 mole of V). [d] Platinum oxide (0.26 g./0.1 mole of V). [e] A reaction was interrupted at an early stage to determine whether the unknown was formed. [f] Uptake complete for 0.1 mole of hydrogen. [g] No uptake was observed using Raney nickel (3–4 g./0.1 mole of V) following B or in alcohol. [h] The compounds are listed in order of their place on the chromatograms run on the Aerograph machine, Model A-90-C. The samples were run on a 3-m. × 0.625-cm. (o.d.) coiled column of 18% silicone L46 and 2% Carbowax 20M on acid-washed 80–100 mesh Chromosorb W. The column was operated at 220°, the injector at 250°. Helium was used as the carrier gas at an inlet pressure of 1.35 kg./cm². II, 2-amino-1-phenylpropane; III, 2-amino-1-(4-chlorophenyl) propane; IV, 2-(N-benzylamino)-1-phenylpropane; V, 2-(N-benzylamino)-1-(4-chlorophenyl)propane. [i] An unknown compound corresponding to about 20–21% of the product submitted was observed in the chromatogram between IV and V. [j] 41–42% of the same unknown. [k] 3–4% of unknown. [l] About 24% of the unknown. So far attempts to isolate it in a preparative chromatographic unit have failed.

of 98.5–99.5% purity. The reduction must be watched, however. In one experiment, about 80% of the dehalogenated product IV was obtained[7] when the reaction was allowed to run too long.

Anal. Calcd. for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; N, 5.39. Found: C, 74.39; H, 6.94; N, 5.39.

Hydrochloride Salt.—The salt may be recrystallized from absolute alcohol or hot water. It first melted at 193–195° but appeared to retain solvent of crystallization. After several days' drying, the melting point was raised to 209–210.5°.

Anal. Calcd. for $C_{16}H_{19}Cl_2N$: C, 64.90; H, 6.46; N, 4.73. Found: C, 64.89; H, 6.31; N, 4.60.

Attempted Debenzylation of V to III. A.—To a solution of 0.36 mole of dry hydrogen chloride in 125 ml. of ethyl alcohol was added 46.71 g. (0.18 mole) of V. Heavy precipitation occurred. The addition of 75 ml. of water did not cause the precipitate to redissolve. Six grams of 5% palladium on carbon was added and the suspension subjected to hydrogenation under 2 kg./cm.² pressure. When uptake of 0.18 mole of hydrogen was complete, the material was filtered and washed with 50% aqueous alcohol until all the insoluble material was dissolved. The solution was then concentrated to dryness under reduced pressure. It was treated with dry benzene and reconcentrated several times to remove any adhering moisture. The dried product weighed 37.7 g., m.p. 187°. After recrystallization from hot absolute ethyl alcohol, it melted at 199–200°.[8]

Anal. Found: C, 72.96; H, 7.65; N, 5.31. Since the halogen contained in the compound is ionic, its values are in close agreement with the calculated values of the hydrochloride salt of IV, $C_{16}H_{20}ClN$: C, 73.36; H, 7.70; N, 5.35.

B.—In another experiment, 25.95 g. (0.1 mole) of V was dissolved in 100 ml. of glacial acetic acid. Hydrogenation was carried out in the presence of 2.6 g. of 5% palladium on carbon under 2–3 kg./cm.² pressure. At the end of 3.5 hr., uptake of 0.1 mole of hydrogen was complete. The solution was filtered from the catalyst and concentrated under reduced pressure. The residue was treated with water and excess sodium hydroxide. The cooled mixture was extracted with either ether or benzene. The extract was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was fractionated. A constant boiling main fraction was collected at 150–153° (3 mm.), $n^{25}D$ 1.5533.[8] The results of elemental analysis indicate that the compound is indeed IV.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.29; H, 8.51; N, 6.22. Found: C, 85.37; H, 8.61; N, 6.29.

A study was made of the attempted debenzylation of V with other catalysts. Following the procedure described in B, the bases before distillation were submitted for vapor phase chromatography. The results are shown in Table I.

Pharmacology.—Compound V, 2-(N-benzylamino)-1-(4-chlorophenyl)propane, as hydrochloride salt, was given orally (in suspension) to three series of 4 rats each at dose levels of 0.011, 0.022, and 0.044 mmole/kg. The food intake was measured in 2 hr. and compared with the controls. Inhibition was 14.3, 28, and 40%, respectively. No central nervous system stimulation was observed at any dose level.

(7) R. Baltzly, *J. Am. Chem. Soc.*, **74**, 4586 (1952), in describing the preparation and properties of platinized charcoal, says it is quite inactive in dehalogenations. The commercial catalyst used in this study may be much more active.

(8) H. Temmler, French Patent 844,228 (July, 1939), gives 170–172° (10 mm.); E. H. Woodruff, J. P. Lambooy, and W. E. Burt, *J. Am. Chem. Soc.*, **62**, 922 (1940), describe the b.p. of N-benzyl-1-methyl-2-phenethylamine as 178° (13 mm.), and the m.p. of the hydrochloride salt as 198–199°.

The Identity of an Alleged Hypocholesteremic Agent Isolated from Bovine Pituitary

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In our continuing search for agents affecting lipid metabolism, we have investigated the nature of a cholesterol-lowering agent reported to be present in both the posterior and anterior lobes of the pituitary gland.[1] This agent has been isolated and a number of physical properties have been determined.[1b]

We have approached the problem by conducting an examination of the nonprotein fractions of the posterior and anterior lobes of beef pituitary. The minced lobes were extracted with acetone at room temperature as described by Wachtel[1b] and the acetone-insoluble fraction was discarded. Chromatography of the extract from the anterior lobe yielded I, m.p. 148–150°, and II, m.p. 84–86°. Chromatography of the extract from the anterior lobe yielded I and II as well as an oily fraction (III), $\nu_{max}^{CHCl_3}$ 1755 cm.$^{-1}$, which had not been detected in the extract from the posterior lobe.

Fraction I was shown to be identical with cholesterol by melting point, mixture melting point, rotation, and infrared spectrum. These parameters, in turn, are virtually identical with those reported for Wachtel's pituitary extract.[1b] It appears that Wachtel's extract is, in fact, cholesterol.

We considered that the dramatic cholesterol-lowering activity reported by Wachtel[1b] might have been due to a contaminant in his cholesterol fraction. We thus examined the biological properties of fractions II and III. The compounds were administered subcutaneously for 7 days to Albino rats of both sexes at a dose level of 25 mg./kg. Both compounds failed to cause a change in the following biochemical parameters determined in the serum: total sterol, glucose, sodium, potassium, uric acid, total nitrogen, and phospholipid. No significant

(1) (a) H. K. Wachtel, *Nature*, **163**, 254 (1949); (b) H. K. Wachtel, U. S. Patent 3,034,963 (May 15, 1962); (c) H. K. Wachtel in "Drugs Affecting Lipid Metabolism," S. Garattini and R. Paoletti, Ed., Elsevier Publishing Co., New York, N. Y., 1961, p. 201.