

ride, but in saturated solution shows only a single sharp 2.79μ band, characteristic of unassociated OH.

Treatment of β -Methylheptenone (I) with 10% Sulfuric Acid.—A 7.0-g. sample of I was shaken with 10% sulfuric acid for 24 hours. Working up in the usual way gave 5.3 g. of material, the infrared spectrum of which showed the absence of characteristic bands for both IIIB and VII. Evaporation of the aqueous phase followed by further extraction gave 0.3 g. of an oil whose infrared spectrum excluded the presence of significant amounts of either diol. No crystalline product could be isolated from this oil.

Treatment of β -Methylheptenone (I) with 20% Sulfuric Acid.—In an experiment carried out exactly as described above for cyclization of V, 21.3 g. of I was treated with 200 ml. of 20% sulfuric acid. After working up in the usual way, 19.3 g. of crude product was obtained. Distillation gave rise to a small amount of 2,2,6-trimethyl-2,3-dihydropyran (VIII) and roughly equal amounts of I and IV. No diol was found either in the distilled IV or in the residue from the distillation.

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[CONTRIBUTION FROM ABBOTT LABORATORIES]

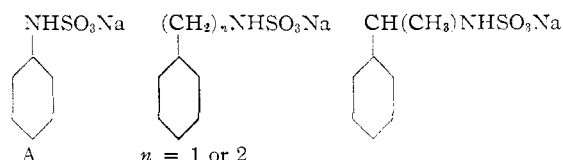
Reductions with Ruthenium Catalysts. I. Preparation of Some Cyclohexylalkylamines¹

BY MORRIS FREIFELDER AND GEORGE R. STONE

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Low pressure hydrogenation of phenylalkylamines to cyclohexylalkylamines with noble metal catalysts is often slow and requires high catalyst ratios to obtain complete reduction. In high pressure hydrogenation of β -phenylalkylamines with Raney nickel, temperature conditions high enough for reduction also cause cracking. Reduction of these aralkylamines in this work with ruthenium gave excellent yields of ring hydrogenated products.

The interest of this Laboratory in sweetening agents led us to prepare some cyclohexylalkylamines as intermediates in the preparation of salts of cyclohexylsulfamic acid² (A) homologs. Our purpose was to observe the change in sweetness when alkylene groups were placed between the nitrogen atom and the saturated ring.

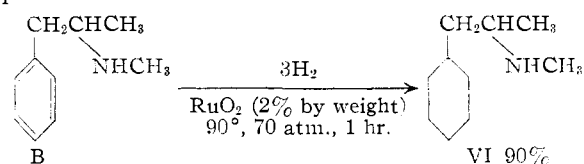


Even though the homologs lacked sweet taste, the unusual results of hydrogenation of the aralkylamines with ruthenium led us to expand the series to cover preparation of β -cyclohexylalkylamines.

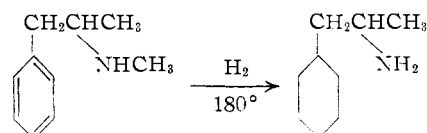
The difficulty in hydrogenating β -phenylalkylamines ($\text{C}_6\text{H}_5\text{CH}_2\text{CHRNR}'$ where R and R' = H or alkyl) has been reported by other investigators. Metayer³ points out that in hydrogenations of phenylalkylamines when the amino group is beta to the aromatic ring, incidental hydrolysis and cracking occur. Zenitz and co-workers⁴ in their study with platinum oxide at low pressure often found it necessary to make additions of catalyst to induce complete hydrogenation. Kindler,⁵ in low pressure hydrogenations with palladium black, used excessively high catalyst ratios (25% by weight of compound) to obtain complete uptake of hydrogen.

In contrast, in this work when ruthenium was used in the hydrogenation of these difficultly reducible β -phenylalkylamines, most reductions were

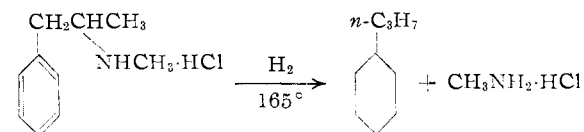
complete within one hour at 90° and 70 atmospheres.



The effect of higher temperature on hydrogenation also was investigated. When the reduction of B was carried out at 120 – 130° , the yield of VI remained at the same high level. At 150° , however, it dropped to 50% and at 180° demethylation accompanied ring reduction.



The hydrochloride of B was also reduced. When the hydrogenation in water or alcohol was carried out under the same conditions described for the base, a comparable yield was obtained. In water, however, when the temperature was raised to 165° , deamination occurred and propylcyclohexane was obtained.



In the reduction of β -phenylalkylamines, the effect of a branched substituent on the ring was noted when the hydrogenation of β -(*p*-isopropylphenyl)-ethylamine was carried out. The time for complete uptake was ten to twelve hours in contrast to the shorter time needed for hydrogenation of the unsubstituted aralkylamines.

l-Ephedrine was hydrogenated to the corresponding cyclohexyl compound without hydrogenolysis of

(1) Presented at the San Francisco Meeting of the American Chemical Society, April, 1958.

(2) Manufactured and sold by Abbott Laboratories under the trade name of Sucaryl Sodium and Sucaryl Calcium.

(3) M. Metayer, *Bull. soc. chim.*, [5] **19**, 276 (1952).

(4) B. L. Zenitz, E. B. Macks and M. L. Moore, *THIS JOURNAL*, **69**, 1117 (1947).

(5) K. Kindler, B. Hedemann and E. Schüffe, *Ann.*, **560**, 215 (1948).

TABLE I^a

No.	Y	Z	Reducn. time, hours	B.p.		<i>n</i> _D ²⁰	Yield, %
				°C.	Mm.		
I	H	-CH ₂ -	0.5	159-161 ^b	760		80
II	H	-CH(CH ₃)-	0.7	68	17	1.4606	72 ^c
III	H	-CH ₂ CH ₂ -	0.5	71-73	13		83
IV	(CH ₃) ₂ CH-	-CH ₂ CH ₂ -	10-12	185-187	760 ^d	1.4626	70 ^e
				101	5	1.4743	

^a Hydrogenation of the aromatic intermediates was carried out at 90° and 70-80 atm. with a 2% ratio of ruthenium dioxide in the absence of solvent. However, for the preparation of IV, methylcyclohexane was used. ^b B.p. 162-164°; Wallach, *Ann.*, **353**, 298 (1907). ^c M.p. of hydrochloride 239-240°. *Anal.* Calcd. for C₈H₁₈ClN: C, 58.70; H, 11.08. Found: C, 58.63; H, 11.14. ^d B.p. 188-189°; Wallach, *Ann.*, **353**, 284 (1907). ^e *Anal.* Calcd. for C₁₁H₂₃N: C, 78.03; H, 13.69. Found: C, 77.93; H, 13.12; m.p. of hydrochloride, 225-227°.

TABLE II^a

No.	R	R'	Reducn. time, hours	B.p.		<i>n</i> _D ²⁰	Yield, %	M.p. hydrochloride, °C.
				°C.	Mm.			
V	H	H	0.15	82-85	15	1.4578	66	191-192 ^b
VI ^c	H	-CH ₃	0.15	74-76	8	1.4570	90	127 ^b
VII	H	-CH ₃ (<i>d</i> -) ^d	1.0	78	8	1.4560	78	137-139 ^b
VIII	H	-CH ₃ (<i>l</i> -) ^d	0.7	80	10	1.4560	81.5	138-139 ^b
IX	-OH	-CH ₃ (<i>l</i> -) ^d	0.7	114-117	8	<i>e</i>	89	201-202
X	H	-C ₆ H ₅	4.0	135	20	1.4590	73.6	127-128

^a Hydrogenation of the aromatic intermediates was carried out at 90° and 70-80 atm. with 2% by weight of ruthenium dioxide. ^b As described by Zenitz, Macks and Moore, *THIS JOURNAL*, **69**, 1117 (1947). ^c Ruthenium-on-carbon (5%) and ruthenium-on-alumina (5%) were also used in the preparation of VI. The time of reduction was increased to 1.5 hours, but the yield was not changed. ^d No change in optical rotation after hydrogenation as reported in references 3, 5, 6. ^e The base solidified on cooling and melted at 60°.

the -OH group and without change in rotation.⁶ In this study, other optically active compounds were hydrogenated without any significant change in activity.^{4,7}

Pressor activity of some of the compounds has been reported.⁴ Compound IX (see Table II) was found by us to be a potent vasopressor. Compound X also listed in Table II and its aromatic intermediate showed a significant drop in blood pressure (-35 to -45 mm.) which returned to normal in one minute.

Acknowledgment.—The authors are indebted to Mr. E. F. Shelberg and his staff for the microanalyses reported in this paper.

Experimental

2-Butylamino-1-cyclohexylpropane. (a) **2-Butylamino-1-phenylpropane.**—A mixture of 67.0 g. (0.5 mole) of phenylacetone and 43.8 g. (0.6 mole) of butylamine in 10 cc. of alcohol was hydrogenated in the presence of 1.4 g. of platinum oxide under a pressure of 3 atmospheres. When hydrogen uptake was completed, the mixture was filtered from the catalyst and the solvent removed. Distillation of the residue yielded 79 g. (82.7%) of product, b.p. 130-137° (20 mm.), *n*_D²⁰ 1.4922.

Anal. Calcd. for C₁₃H₂₁N: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.25; H, 10.95; N, 7.68.

A hydrochloride salt was prepared which melted at 172°.

(6) German Patent Application, H. Metzger, March 29, 1956, reported hydrogenation of *l*-ephedrine, in the presence of platinum oxide to *l*-cyclohexylisopropylmethylamine. With palladium black, hydrogenation was accompanied by reversal of rotation.

(7) W. Leithe, *Ber.*, **65**, 665 (1932), reported occurrence of racemization when *l*- α -phenethylamine, [α]_D²⁰ -40.8°, was hydrogenated to α -cyclohexylethylamine, [α]_D²⁰ +3.2°. Zenitz and co-workers reported reversal of rotation in hydrogenations of *d*- and *l*-1-phenylisopropylmethylamine.

Anal. Calcd. for C₁₃H₂₂ClN: C, 68.55; H, 9.74; N, 6.15; Cl, 15.56. Found: C, 68.91; H, 9.81; N, 6.10; Cl, 15.55.

(b) **2-Butylamino-1-cyclohexylpropane.**—2-Butylamino-1-phenylpropane (40.2 g., 0.22 mole) was hydrogenated under 70 atmospheres pressure at 90° in the presence of 0.8 g. of ruthenium dioxide.⁸ After removal of catalyst and distillation of the residue, a yield of 30.4 g. (73.6%) was obtained, b.p. 130-133.5° (20 mm.), *n*_D²⁰ 1.4540.

Anal. Calcd. for C₁₃H₂₇N: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.41; H, 13.76; N, 7.32.

A hydrochloride salt was prepared which melted at 127-128°. *Anal.* Calcd. for C₁₃H₂₈ClN: C, 66.77; H, 12.07; N, 5.99. Found: C, 66.88; H, 11.88; N, 5.91.

1-2-Amino-1-cyclohexyl-1-hydroxypropane.—A solution of 82.6 g. (0.5 mole) of *l*-ephedrine in 250 cc. of absolute ethanol was hydrogenated under 80 atmospheres at 90° in the presence of 1.6 g. of ruthenium dioxide. The calculated drop in pressure was reached in 40 minutes. When the reaction mixture was cooled to room temperature, the solution was filtered from the catalyst and the solvent distilled. The residue was then distilled to yield 76 g. (89%) of product which boiled at 114-117° (8 mm.) and melted at 60°. The hydrochloride melted at 201-202°.

Anal. Calcd. for C₁₀H₂₂ClNO: C, 57.81; H, 10.68; N, 6.74. Found: C, 58.08; H, 10.73; N, 6.68.

Higher Temperature Hydrogenations. Reduction of 2-Methylamino-1-phenylpropane.—2-Methylamino-1-phenylpropane (74.6 g. 0.5 mole) was placed in a 1-l. bomb and hydrogenated in the presence of 0.37 g. of ruthenium dioxide at 180° and 100 atmospheres. In 10 minutes, uptake of hydrogen stopped. After cooling, the residue freed from catalyst was distilled, b.p. 87-94° (20 mm.), *n*_D²⁰ 1.4560; 61 g. of product was obtained. A portion was converted to a hydrochloride, m.p. 192°, and analyzed. Calcd. for C₉H₂₀ClN: C, 60.82; H, 11.34; Cl, 19.95. Found: C, 61.07; H, 11.13; Cl, 20.11. A mixed melting point with an authentic sample of 2-amino-1-cyclohexylpropane hydrochloride was not depressed.

Reduction of Hydrochloride.—The hydrochloride (92.8 g., 0.5 mole) dissolved in 250 cc. of water was placed in a 1-l.

(8) The ruthenium catalysts used in this work were obtained from Baker and Co., 113 Astor St., Newark, N. J.

bomb and hydrogenated under 100 atmospheres pressure at 165° in the presence of 0.93 g. of ruthenium dioxide. Uptake of hydrogen did not proceed to completion because of the oily hydrogenolysis product which coated the catalyst. After filtration from the catalyst, the oily material was extracted with ether and distilled; 16 g. of a product boiling

at 55–58° (20 mm.), 153–160° (760 mm.), n_D^{20} 1.4356 was obtained.

Anal. Calcd. for C_6H_{18} (propylcyclohexane): C, 85.63; H, 14.37. Found: C, 85.93; H, 14.63.

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[CONTRIBUTION FROM GEORGE HERBERT JONES LABORATORY AND THE ARGONNE CANCER RESEARCH HOSPITAL, UNIVERSITY OF CHICAGO]

Platinum-catalyzed Exchange of Aromatic Compounds with Deuterium Oxide

BY W. G. BROWN AND J. L. GARNETT

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An exchange reaction, using heavy water and catalyzed by active platinum, has been applied to the deuteration of benzoic acid and its sodium salt, bromobenzene, isopropyl benzoate, aniline, nitrobenzene, *p*-nitrobenzoic acid and trimesic acid. Exchange with sodium benzoate involves an apparent induction period, followed by rapid deuteration and eventually complete equilibration with respect to all ring positions. Differences in deuteration rate have been observed for the various compounds. An initial orientation effect occurs in the deuteration of sodium benzoate.

Introduction

A procedure has been devised by Leitch¹ for the preparation of benzene- d_6 which employs the platinum-catalyzed exchange reaction of benzene with deuterium oxide at 110°. In convenience and in freedom from side reactions, the method is superior to the vapor phase exchange on nickel at higher temperatures,² and, for similar reasons, it is to be preferred over the older method based upon the exchange of benzene with deuterio-sulfuric acid.³ The possible extension of the liquid phase platinum-catalyzed exchange reaction to the deuteration of other aromatic compounds was of interest to us, especially with reference to benzene derivatives, *e. g.*, benzoic acid, not readily deuterated by alternative methods. The benzene derivatives used in this series of exchange reactions were benzoic acid, sodium benzoate, bromobenzene, isopropyl benzoate, aniline, nitrobenzene, *p*-nitrobenzoic and trimesic acids.

Experimental

Analytical Procedure for Deuterium.—The Graff and Rittenberg⁴ method was used for deuterium analyses. Before combustion, each sample was diluted with non-isotopic material to give an α -value of 0.65–0.70 [α = m.e.D/m.e. (D + H)]. Accuracy to 1% deuterium was achieved in the analytical procedure, the mass spectrometer being calibrated against standard deuterium samples.

Deuteration Procedure.—The general technique adopted for the exchange experiments will be illustrated with reference to benzoic acid and aniline.

Benzoic Acid.—A solution of 130 mg. of sodium benzoate in 390 mg. of deuterium oxide (99.5%) was added to 100 mg. of heavy water containing 12 mg. of catalyst (platinum oxide which had been pre-reduced with deuterium). The Pyrex tube containing the reactants was frozen in a Dry Ice-acetone-bath, vacuum sealed and shaken at 130–135° for the required time. The tube was cooled, opened, the contents reheated to 80° and filtered hot to remove the catalyst. The filtrate was acidified with dilute hydrochloric acid, the precipitate sublimed once, then recrystallized twice from 25% aqueous methanol to yield 80.0 mg. of benzoic acid (deuterium analysis shown in Table I).

Substantially pure benzoic acid- d_6 was prepared in the following manner. Three successive equilibrations of benzoic acid with heavy water were performed and the product after these exchange reactions recrystallized twice from 25% aqueous methanol, thus removing any exchangeable deuterium which had been present in the carboxylic acid group.

Aniline.—A mixture of 392 mg. of aniline (distilled twice before use), 2.2 g. of heavy water and 30 mg. of pre-reduced platinum oxide were shaken in an evacuated tube at 130° for 24 hours. The tube was cooled, opened and 400 mg. of benzene added. The benzene layer was extracted with dilute NaOH to remove traces of phenol, washed well with water, distilled under atmospheric pressure to remove benzene and water, and then under reduced pressure. A second vacuum distillation was performed to provide 300 mg. of deuterated aniline (deuterium analysis shown in Table I). Infrared techniques were used to ensure that all exchangeable deuterium (as N-D) was removed by washing the deuterated aniline with water before the distillation step. The product from the exchange reaction was then $C_6D_5-NH_2$ (aniline- d_5).

To prepare the tribromo derivative, bromine (0.03 ml.) was added to aniline- d_5 (10 mg.) dissolved in glacial acetic acid (0.2 ml.), the tube shaken for several minutes, diluted with water (0.1 ml.), cooled and centrifuged. The resulting 2,4,6-tribromoaniline, twice recrystallized from aqueous methanol, m.p. 120–121°, contained approximately 40% (based upon infrared C-D intensities) of the deuterium present in the deuterated aniline. Since care was taken to ensure that no exchangeable D was present (as N-D) in the deuterated aniline before bromination, it can be concluded that 40% of the original ring deuterium present was in the *m*-position.

Results and Discussion

Directive effects of substituents, with resultant unequal rates of exchange at non-equivalent ring positions, have already been observed in the nickel-catalyzed exchange reactions of some aromatic compounds. Lauer and Errede⁵ reported that the *o*-hydrogens of aniline exchanged more readily than did the *m*- and *p*-hydrogens. Tiers⁶ noted differences in the rates of exchange of the ring hydrogens of toluene with heavy water and Bonner⁷ has studied the exchange of the ring hydrogens of 2-phenylpropionamide in deuterioethanol with Raney nickel. In both of these instances the *o*-positions proved to be somewhat less reactive than other ring positions. The effects of this kind

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