$$I_2 = \frac{I_1}{1 + \frac{e^{-63,000/T}e^{199.86}e^{-69,000/T}e^{-183.1}}{1 + e^{-63,000/T}e^{199.86}} \cdot U^{2.50}} = \frac{I_1}{1 + \frac{e^{-4,000/T}e^{16.76}}{1 + e^{-63,000/T}e^{199.86}} U^{2.50}} \quad (8b)$$

in which I_1 has been calculated by equation (2b).

Discussion

A comparison between the theoretical and experimental points in Figs. 1 and 2 indicates essentially good agreement at suboptimal temperatures, and at the lower concentrations of urethan. At temperatures above the optimum, especially in higher concentrations of urethan, the predicted rates are generally too high. These facts suggest that the discrepancies are, in part at least, due to an additional inhibition, possibly an irreversible denaturation, that is not taken into account by the theory. Possibly for the same reason, the experimentally observed lowering of the optimal temperature in the presence of urethan is not predicted by the calculated curves, although such a prediction in change in optimal temperatures would result with a greater difference in the constants ΔH_1 and ΔS_1 in comparison with ΔH_3 and ΔS_3, respectively. It may be significant also that the experimental points at 18° in Fig. 1 and at 15° in Fig. 2 are high in comparison with the theoretical curve. The interpretation is uncertain, however, and would require further studies through a range of still lower temperatures.

The similarity between $\Delta H‡$ values for oxygen uptake and MB reduction (13,400 and 13,600 calories, respectively), in addition to the observation that the inhibition of both processes by a given concentration of urethan and at a given temperature is nearly the same, suggests that the anaerobic dehydrogenase is very largely the limiting system in the total oxygen consumption and that the action of urethan is primarily on that system. Differences in the values of ΔH_3 and of ΔS_3 for oxygen uptake and MB reduction possibly originate, in part, to differences in *p*H of the medium used. In view of the relatively anaerobic conditions which exist in the nodules, the importance of dehydrogenases in the respiratory mechanism of root nodule bacteria is plausible. A fraction of the total oxygen consumption probably goes through a urethan-insensitive system as the inhibition of oxygen uptake was somewhat less than that of MB reduction.

Summary

Respiratory experiments with *Rhizobium trifolii* 209 suggest that urethan inhibits its uptake of oxygen and reduction of methylene blue by influencing a denaturation equilibrium that exists between native and denatured enzymes. At suboptimal temperatures urethan promotes the reversible denaturation of one or more critical enzymes, thus decreasing the concentration of active catalysts. As the temperature is increased beyond a threshold value that varies with the concentration of urethan, this reversible denaturation is increasingly accompanied by an irreversible denaturation, and the inhibition by urethan becomes progressively more pronounced.

The fact that this interpretation agrees satisfactorily with the quantitative implications of the theory of absolute reaction rates provides further evidence for the applicability of that theory to general biological problems.

MADISON, WISCONSIN RECEIVED NOVEMBER 29, 1946

[CONTRIBUTION FROM THE SCIENTIFIC LABORATORIES, FREDERICK STEARNS & COMPANY, DIVISION OF STERLING DRUG INC.]

Preparation of Some Primary and Secondary β-Cyclohexylalkylamines[1]

BY BERNARD L. ZENITZ, ELIZABETH B. MACKS AND MAURICE L. MOORE

Since it has been well established that the β-phenylethylamine skeleton is closedly associated with sympathomimetic activity, it was of interest to determine how this relationship would be affected by a replacement of the phenyl nucleus by a cyclohexyl radical.

Though a large number of compounds containing a β-cyclohexylethylamine grouping have been prepared in the antispasmodic field,[1,2,3,4] only a comparatively few of them have been pharmacologically investigated for sympathomimetic activity.[5,6,7]

Therefore, we prepared for further physiological study the series of β-cyclohexylalkylamines listed in Table I. Of this series, the syntheses of I, II, III and IV only have been described previously.[1,8,9,10]

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society meeting, Chicago, Illinois, September 13, 1946.

(1a) Blicke and Monroe, THIS JOURNAL, **61**, 91 (1939).

(2) Blicke and Zienty, *ibid.*, **61**, 93 (1939): **61**, 771 (1939); **61**, 774 (1939).

(3) Blicke, U. S. Patent 2,180,344, Nov. 21, 1939.

(4) Heyn, U. S. Patent 2,278,123, March 31, 1942.

(5) Gunn and Gurd, *J. Physiol.*, **97**, 453 (1940).

(6) Shonle and Rohrmann, New York Meeting of the American Chemical Society, Division of Medicinal Chemistry, 1944.

(7) Lands, Lewis and Nash, *J. Pharmacol. Exptl. Ther.*, **83**, 253 (1945).

(8) Wallach, *Ann.*, **353**, 284 (1907).

(9) Coleman and Adams, THIS JOURNAL, **54**, 1982 (1932).

(10) Levene, Mikeska and Passoth, *J. Biol. Chem.*, **88**, 27 (1930).

TABLE I

β-CYCLOHEXYLALKYLAMINES PREPARED BY HYDROGENATION OF β-PHENYLALKYLAMINES

No.	C_6H_{11}—R, R =	B. p., °C.	Mm.	n^{20}	Yield, %	Formula	Nitrogen, % Calcd.	Found	Hydrochloride M. p., °C.	Formula	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
I	$-CH_2CH_2NH_2$[a]	83–85	25	1.4656	78.6	$C_8H_{17}N$	11.01	11.22	254–256[a]	$C_8H_{18}NCl$	8.56	8.60	21.66	21.65
II	$-CH_2CH_2NHCH_3$[b]	77–78	9	1.4586	85.1	$C_9H_{19}N$	9.92	9.85	171–172[b]	$C_9H_{20}NCl$	7.88	7.89	19.95	20.12
III	$-CH_2CH_2NHC_2H_5$[c]	87–88	10	1.4582	77.4	$C_{10}H_{21}N$	9.02	9.06	231–233[c]	$C_{10}H_{22}NCl$	7.31	7.37	18.49	18.67
IV	$-CH(CH_3)CH_2NH_2$[d]	90–91.5	17	1.4718	86.0	$C_9H_{19}N$	9.92	10.02	194–196	$C_9H_{20}NCl$	7.88	7.98	19.95	19.96
V	$-CH(CH_3)CH_2NHCH_3$	90–91	12	1.4646	87.1	$C_{10}H_{21}N$	9.02	8.90	204–205	$C_{10}H_{22}NCl$	7.31	7.32	18.49	18.49
VI	$-C(CH_3)_2CH_2NH_2$	86–88	7	1.4752	80.7	$C_{10}H_{21}N$	9.02	9.01	206–207	$C_{10}H_{22}NCl$	7.31	7.12	18.49	18.39
VII	$-C(CH_3)_2CH_2NHCH_3$	92–93	8	1.4694	80.0	$C_{11}H_{23}N$	8.27	8.28	266–268	$C_{11}H_{24}NCl$	6.81	6.84	17.23	17.21
VIII	$-CH_2CH(NH_2)CH_3$	85–87	21	1.4615	76.9	$C_9H_{19}N$	9.92	10.06	191–192	$C_9H_{20}NCl$	7.88	8.01	19.95	19.94
IX	$-CH_2CH(NHCH_3)CH_3$	92–93	20	1.4600	85.6	$C_{10}H_{21}N$	9.02	9.08	127–128	$C_{10}H_{22}NCl$	7.31	7.44	18.49	18.32
X	$-CH_2CH(NHCH_3)CH_3$ (*d*-)[e]	82–83	10	1.4588	82.1	$C_{10}H_{21}N$	9.02	9.04	138–139	$C_{10}H_{22}NCl$	7.31	7.45	18.49	18.57
XI	$-CH_2CH(NHCH_3)CH_3$ (*l*-)[e]	80–81	9	1.4590	80.7	$C_{10}H_{21}N$	9.02	9.05	138–139	$C_{10}H_{22}NCl$	7.31	7.50	18.49	18.61
XII	$-CH(CH_3)CH(NH_2)CH_3$	94–96	14	1.4730	77.2	$C_{10}H_{21}N$	9.02	8.86	197–198 (A)	$C_{10}H_{22}NCl$	7.31	7.31	18.49	18.48
									145–146 (B)	$C_{10}H_{22}NCl$	7.31	7.29	18.49	18.64
XIII	$-CH(CH_3)CH(NHCH_3)CH_3$	93–94	8	1.4710	85.6	$C_{11}H_{23}N$	8.27	8.29	152–153 (A)	$C_{11}H_{24}NCl$	6.81	6.88	17.24	17.26
									128–130 (B)	$C_{11}H_{24}NCl$	6.81	6.90	17.24	17.07
XIV	$-C(CH_3)_2CH(NH_2)CH_3$	109–111	16	1.4758	69.4	$C_{11}H_{23}N$	8.27	8.27	124.5–126	$C_{11}H_{24}NCl$	6.81	6.97	17.24	17.32
XV	$-C(CH_3)_2CH(NHCH_3)CH_3$	106–108	10	1.4752	73.8	$C_{12}H_{25}N$	7.68	7.77	202–204	$C_{12}H_{26}NCl$	6.37	6.51	16.13	16.14

[a] B. p. of base, 188–189°, m. p. of hydrochloride 252–253°, Wallach, *Ann.*, **353**, 284 (1907). M. p. of hydrochloride, 245–246°, Coleman and Adams, THIS JOURNAL, **54**, 1982 (1932). [b] B. p. 89–90° at 14 mm., (base), m. p. 169–170 (hydrochloride), ref. 1. [c] B. p. 100–105° at 21 mm., (base), m. p. 231–232 (hydrochloride), ref. 1. [d] B. p. 65–66° at 2 mm., Levene, Mikeska and Passoth, *J. Biol. Chem.*, **88**, 27 (1930). Forms a benzamide with benzoyl chloride in pyridine, m. p. 89–90°. [e] The *d*-isomer (hydrochloride, $\alpha^{26}D$ +14.73° in water) was obtained from 1-N,α-dimethyl-β-phenylethylamine and the *l*-isomer (hydrochloride, $\alpha^{26}D$ −14.74° in water) from *d*-N, α-dimethyl-β-phenylethylamine, a reversal of rotational sign having been produced by the hydrogenation of the phenyl to the cyclohexyl group. Leithe, *Ber.*, **65**, 660 (1932), observed a similar reversal in the hydrogenation of 1-α-phenylethylamine.

All of the cyclohexyl bases were obtained by the catalytic hydrogenation of their phenyl analogs

$$C_6H_5C(R_1R_2)CH(R_3)NHR_4 \xrightarrow[PtO_2]{H_2} C_6H_{11}C(R_1R_2)CH(R_3)NHR_4$$

(R_1, R_2 and R_3 = H or CH_3; R_4 = H, CH_3 or C_2H_5)

Initial attempts to hydrogenate the hydrochlorides of the intermediate phenyl bases in aqueous solution with Adams platinum catalyst at room temperature and sixty pounds pressure proved unsatisfactory. Under these conditions the absorption of hydrogen was generally very slow and incomplete. However, when the free bases were used with glacial acetic acid as the solvent, reduction to the cyclohexyl derivatives was successfully accomplished.

The phenylalkylamine intermediates have been previously described in the literature and were obtained either from commercial sources or were synthesized by known procedures.

No attempt was made to separate the two possible racemic mixtures of either α,β-dimethyl-β-phenylethylamine or N,α,β-trimethyl-β-phenylethylamine before hydrogenation, but their cyclohexyl derivatives (XII and XIII) were each obtained in two racemic forms by the fractional recrystallization of their hydrochlorides.

In order to demonstrate that the hydrogenation procedure did not alter the alkylamine side chain, four of the cyclohexyl bases (II, III, IV and V) were also prepared by the procedures indicated below:

(A) $C_6H_{11}CH_2CH_2Br \xrightarrow{RNH_2} C_6H_{11}CH_2CH_2NHR$ (R = CH_3 and C_2H_5)
II and III

(B) $C_6H_5C(CH_3)=CHCOOH \xrightarrow[PtO_2]{H_2} C_6H_{11}CH(CH_3)CH_2COOH \xrightarrow{SOCl_2}$
XVI
$C_6H_{11}CH(CH_3)CH_2COCl \xrightarrow{NH_3}$
XVII
$C_6H_{11}CH(CH_3)CH_2CONH_2 \xrightarrow[NaOH]{Br_2}$
XVIII
$C_6H_{11}CH(CH_3)CH_2NH_2 \xrightarrow{C_6H_5CHO}$
IV
$C_6H_{11}CH(CH_3)CH_2N=CHC_6H_5 \xrightarrow[(2)\ HOH]{(1)\ CH_3I}$
XIX
$C_6H_{11}CH(CH_3)CH_2NHCH_3$
V

The cyclohexyl bases so obtained were identical with those prepared by hydrogenation as was shown by a comparison of their physical constants and by mixed melting points of their hydrochlorides.

Pharmacology

Pressor Activity.—Examination of the pharmacological data summarized in Table II leads to the following conclusions:

1. The highest activity of the series is produced with N-methyl-β-cyclohexylethylamine (II). Thus N-methylation of the primary amine (I) increases pressor potency, as well as toxicity; while N-ethylation only slightly decreases pressor activity. This is contrary to the effects of N-alkylation in the phenyl series; there the N-methylation of β-phenylethylamine decreases ac-

TABLE II

PRESSOR ACTIVITY AND TOXICITY OF β-CYCLOHEXYLALKYLAMINES[a]

No.	C_6H_{11}—R.[b] R =	Pressor activity[c]	Duration. min.	Approx. toxicity L. D_{50} mg./kg. i. p. mouse
I	$-CH_2CH_2NH_2$	1.0	3–4	140
II	$-CH_2CH_2NHCH_3$[d]	0.6	3–4	118
III	$-CH_2CH_2NHC_2H_5$	1.1	3–4	100
IV	$-CH(CH_3)CH_2NH_2$	1.3	4–7	100
V	$-CH(CH_3)CH_2NHCH_3$	1.2	5–15	100
VI	$-C(CH_3)_2CH_2NH_2$	1.3	10–15	70
VII	$-C(CH_3)_2CH_2NHCH_3$	Weak	Prolonged	90
VIII	$-CH_2CH(CH_3)NH_2$	0.8	6–35	60
IX	$-CH_2CH(CH_3)NHCH_3$	0.9	Prolonged	70
X	$-CH_2CH(CH_3)NHCH_3$ (*d*-)	1.2	Prolonged	70
XI	$-CH_2CH(CH_3)NHCH_3$ (*l*-)	0.6	Prolonged	70
XIIA	$-CH(CH_3)CH(CH_3)NH_2$	1.4	Prolonged	100
XIIB	$-CH(CH_3)CH(CH_3)NH_2$	1.9	Prolonged	80
XIIIA	$-CH(CH_3)CH(CH_3)NHCH_3$	Weak	Prolonged	70
XIIIB	$-CH(CH_3)CH(CH_3)NHCH_3$	Weak	Prolonged	90
XIV	$-C(CH_3)_2CH(CH_3)NH_2$	Weak	Prolonged	50
XV	$-C(CH_3)_2CH(CH_3)NHCH_3$	Weak[e]	Prolonged	80

[a] We are indebted to the pharmacology staff of Frederick Stearns & Co. Division for the pressor and toxicity data. [b] All the amines except X and XI were the *dl* isomers. [c] Expressed as the dose equivalent to 1 mg. of $C_6H_{11}CH_2CH_2NH_2$. All of the amines were tested as 1% aqueous solutions of their hydrochloride salts in dogs anesthetized with sodium pentobarbital. The amines containing an isopropylamine side chain (VIII to XV) showed marked tachyphylaxis and great variability from animal to animal which makes an accurate evaluation of activity difficult. [d] Approximately 1/250 as active as epinephrine (ref. 7). [e] Produces a slight fall in blood pressure in some animals.

tivity,[11] while N-ethylation practically destroys it, producing a compound of unpredictable action which gives a slight rise in pressure in some animals and a fall in others.[7]

2. The introduction into β-cyclohexylethylamine (I) of either an α-methyl or both an α-methyl and an N-methyl group (VIII and IX) also increases activity, but at the same time the toxicity is increased.

3. The introduction of a β-methyl group into the β-cyclohexylethylamine structure (I and II) to produce compounds (IV and V), or into the β-cyclohexylisopropylamine structure (VIII and IX) to produce (XII and XIII), decreases pressor potency in each case. A second β-methyl substitution produces a still further decrease in activity.

4. With the exception of VII, all of the amines lacking an α-methyl group (I to VI) show a comparatively short duration of activity; this group seems to be necessary for a prolongation of the pressor effect. The duration of activity of the β-cyclohexylalkylamines is comparable to their corresponding phenyl analogs.[11]

Central Nervous System Stimulation.—Since the phenyl analogs of several of the amines of our series are known to produce central nervous system stimulation (C. N. S. effect), and in view of the report of Gunn and Gurd[5] that "when compounds with corresponding side chains are compared, the cyclohexyl nucleus seems to be slightly more stimulant than the phenyl nucleus," a number of the amines of our series were tested for their C.N.S. effects. The data are summarized in Table III.

(11) Lands, Department of Pharmacology, Frederick Stearns & Company Division, personal communication.

TABLE III

CENTRAL NERVOUS SYSTEM STIMULATION[a]

No.	C_6H_5—R.[b] R=	Dose. mg./kg.	C. N. S. stim.[d] rats
XX	$-CH_2CH_2(CH_3)NH_2$	1.0	+
	$-CH_2CH_2(CH_3)NH_2$	2.5	++
XXI	$-CH_2CH_2(CH_3)NHCH_3$ (*d*-)	1.0	++++
	$-CH_2CH_2(CH_3)NHCH_3$	2.5	+++++
	C_6H_{11}—R[c]. R =		
II	$-CH_2CH_2NHCH_3$	2.5	0
	$-CH_2CH_2NHCH_3$	20.0	±
	$-CH_2CH_2NHCH_3$	30.0	±
V	$-CH(CH_3)CH_2NHCH_3$	5.0	0
	$-CH(CH_3)CH_2NHCH_3$	30.0	+
VI	$-C(CH_3)_2CH_2NH_2$	5.0	+
	$-C(CH_3)_2CH_2NH_2$	20.0	+
VII	$-C(CH_3)_2CH_2NHCH_3$	10.0	±
	$-C(CH_3)_2CH_2NHCH_3$	20.0	±
VIII	$-CH_2CH(CH_3)NH_2$	5.0	+
	$-CH_2CH(CH_3)NH_2$	30.0	+
IX	$-CH_2CH(CH_3)NHCH_3$	5.0	0
	$-CH_2CH(CH_3)NHCH_3$	30.0	+±
X	$-CH_2CH(CH_3)NHCH_3$ (*d*-)	20.0	+
XI	$-CH_2CH(CH_3)NHCH_3$ (*l*-)	2.5	±
	$-CH_2CH(CH_3)NHCH_3$ (*l*-)	5.0	++
XIIA	$-CH(CH_3)CH(CH_3)NH_2$	5.0	0
	$-CH(CH_3)CH(CH_3)NH_2$	20.0	+±
XV	$-C(CH_3)_2CH(CH_3)NHCH_3$	10.0	0
	$-C(CH_3)_2CH(CH_3)NHCH_3$	20.0	0

[a] We are indebted to the Department of Pharmacology, Sterling-Winthrop Research Institute, for these data. [b] Included for comparison. [c] All the amines except X and XI were the *dl* isomers. [d] Determined by the increase in the random activity of rats after subcutaneous injection as measured by revolutions/hour in a "Jiggle cage." Amine XX was tested as its sulfate salt; the other amines, as their hydrochloride salts.

All of the cyclohexylalkylamines tested were less stimulating than amphetamine (XX), and none, in a dose of 20 or 30 mg./kg. subcutaneously, increased the activity nearly as much as 1 mg./kg. of *d*-desoxyephedrine (XXI).

Experimental

All recorded melting and boiling points are uncorrected.

Catalytic Hydrogenations.—One-tenth mole of the β-phenylalkylamine in 150 ml. of glacial acetic acid was hydrogenated with 0.5 g. of Adams platinum oxide catalyst at an initial pressure of 60 pounds. Except in the case of α,β,β-trimethyl-β-phenylethylamine (which was run at 80°), all of the hydrogenations were carried out at room temperature. Additional catalyst (0.3 to 0.4 g.) was added from time to time whenever the hydrogen addition became extremely sluggish.

After the theoretical amount of hydrogen had been absorbed, and hydrogenation had ceased, the catalyst was filtered and the solvent was removed under reduced pressure. An excess of 30% sodium hydroxide solution was added to the residual sirup and the free amine, which separated as an oil, was extracted with ether. The ether

solution was washed with water and dried over anhydrous sodium carbonate.

After removal of the ether by distillation, the residual oil was distilled *in vacuo* through a column to give the cyclohexylalkylamine as a colorless oil. The experimental data are recorded in Table I.

β-Cyclohexylalkylamine Hydrochlorides.—The experimental data for these hydrochlorides are given in Table I.

Dry hydrogen chloride was passed into a solution of 5 g. of α,β-dimethyl-β-cyclohexylethylamine (XII) in 150 ml. of anhydrous ether and the solution was kept in the refrigerator overnight. The precipitate was filtered and the ether filtrate was set aside. Recrystallization of the precipitate from a mixture of 2-propanol and *i*-propyl ether gave the higher melting isomer (A). The lower melting isomer (B) was obtained from the ether filtrate by distillation of the ether and recrystallizing the residue three times from 100-ml. portions of *i*-propyl ether followed by repeated recrystallizations from 15-ml. portions of ethyl acetate until the melting point was constant.

The other fourteen amines were converted into their hydrochlorides by dissolving them in *i*-propyl ether and passing dry hydrogen chloride into the solutions. Fractional recrystallization from ethyl acetate of the precipitate obtained from α,β,N-trimethyl-β-cyclohexylethylamine (XIII) yielded the two racemates (A) and (B). In conformity with their structures, recrystallization from a 2-propanol-*i*-propyl ether mixture of the other precipitated hydrochlorides gave only one product in each case.

Preparation of β-Cyclohexylalkylamines from Cyclohexyl Intermediates

N-Methyl-β-cyclohexylethylamine (II).—To a solution of 124 g. (4.0 moles) of methylamine in 300 ml. of ethanol was added 191.1 g. (1.0 mole) of β-cyclohexylethyl bromide. After twenty-four hours in a stoppered citrate bottle at room temperature, the ethanol was distilled through a column from a steam-bath, using reduced pressure toward the end of the distillation. A mixture of 175 ml. of concentrated hydrochloric acid and 425 ml. of water was added to the residue and the mixture was cooled to 5–10°. The insoluble N-methyl-di-(β-cyclohexylethyl)-amine hydrobromide was filtered and washed with water.

The aqueous filtrate and washings were combined, concentrated on a steam-bath under reduced pressure to about 500 ml. and washed with ether to remove any unreacted bromide. The solution was then stirred in an ice-bath and was made basic by the careful addition of sodium hydroxide pellets. The free amine which separated as an oil was extracted with ether. After washing the ether solution with water and drying over anhydrous sodium carbonate, the ether was distilled. Distillation of the residual oil through a column gave the amine as a colorless oil in a yield of 73.7%, b. p. 71–72° at 7 mm., n^{20} 1.4590. It formed a hydrochloride with hydrogen chloride in ether which, after recrystallization from a mixture of 2-propanol and ether, melted at 171–172°.

N-Ethyl-β-cyclohexylethylamine (III).—A mixture of 129.9 g. (0.68 mole) of β-cyclohexylethyl bromide and 108 g. (2.4 moles) of ethylamine in 200 ml. of chloroform was allowed to stand at room temperature in a tightly stoppered citrate bottle for three days. The solvent was then distilled under reduced pressure through a column from a steam-bath.

A mixture of 140 ml. of concentrated hydrochloric acid and 450 ml. of water was added to the residue. The crystalline precipitate which separated upon cooling the mixture to 10° proved to be N-ethyl-β-cyclohexylethylamine hydrobromide. No tertiary amine was isolated.

The aqueous filtrate was washed with ether and was recombined with the precipitate. This mixture was stirred, cooled and made basic by the addition of sodium hydroxide pellets. The free amine, which separated as an oil, was further purified as described for the N-methyl compound and was obtained as a colorless oil in a yield of 63.2%, b. p. 83° at 8 mm., n^{20} 1.4580.

Its hydrochloride, after recrystallization from alcohol-ether, melted at 231–233°.

β-Cyclohexylbutyric Acid (XVI).—A solution of 48.6 g. (0.3 mole) of β-methylcinnamic acid[12] in 175 ml. of glacial acetic acid was hydrogenated at room temperature and at an initial pressure of 60 pounds with 0.4 g. of Adams platinum oxide catalyst. Additional catalyst was added to increase the rate of hydrogenation when it became necessary. The theoretical amount of hydrogen was absorbed in about twenty-four hours and the hydrogenation then ceased. The catalyst was filtered and the solvent was removed under reduced pressure. Distillation of the residual oil *in vacuo* through a Claisen head gave the reduced acid in a 95% yield as a colorless oil, b. p. 160–161° at 14 mm.[13]

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65. Found: C, 70.42; H, 10.56.

β-Cyclohexylbutyryl Chloride (XVII).—The acid (XVI) (86 g., 0.5 mole) was dropped into 71.4 g. (0.6 mole) of refluxing thionyl chloride over a half hour period. After refluxing for an additional forty-five minutes, the reaction mixture was distilled *in vacuo* through a column. The acid chloride was obtained in a yield of 96% as a colorless oil, b. p. 113–114° at 12 mm.

β-Cyclohexylbutyramide (XVIII).—The acid chloride (155.8 g., 0.825 mole) was dropped into 800 ml. of 28% ammonia water which was stirred and cooled in an ice-bath. The precipitated amide was filtered, washed with water, dried and recrystallized from 350 ml. of toluene; m. p. 122–123°; yield 94.5%.

Anal. Calcd. for $C_{10}H_{19}ON$: N, 8.27. Found: N, 8.46.

β-Methyl-β-cyclohexylethylamine (IV).—Bromine (83.2 g., 0.52 mole) was dropped into a stirred suspension of 84.6 g. (0.5 mole) of the amide (XVIII) in 480 ml. of 10% sodium hydroxide (1.2 moles) kept at 0–5° by an ice-acetone bath. The resulting yellow solution, containing a small amount of insoluble material, was then poured into a rapidly stirred solution of 112 g. (2.8 moles) of sodium hydroxide in 160 ml. of water, previously heated to 100°. The mixture was vigorously stirred for two and a half hours at 80–85° and was then steam distilled.

The amine was extracted from the distillate with ether. After drying the ether solution over anhydrous sodium carbonate, the ether was distilled. Distillation of the residual oil through a column *in vacuo* gave the amine as a colorless oil in a yield of 56.6%, b. p. 83–84° at 10 mm., n^{20} 1.4700.

Treatment of the amine base in *i*-propyl ether with hydrogen chloride gave the hydrochloride; m. p. 199–200° after recrystallization from a mixture of 2-propanol and *i*-propyl ether.

The benzamide derivative of the amine, prepared in pyridine with benzoyl chloride, melted at 89–90° after recrystallization from dilute alcohol.

Anal. Calcd. for $C_{16}H_{23}NO$: N, 5.71. Found: N, 5.67.

N,β-Dimethyl-β-cyclohexylethylamine (V).—The primary amine (IV) was methylated by the Decker and Becker method described by Woodruff, Lambooy and Burt.[14] The intermediate Schiff base (XIX) was obtained from 14.1 g. (0.1 mole) of IV and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde, as a viscous pale yellow oil in a yield of 86%, b. p. 126–127° at 0.7 mm.

Anal. Calcd. for $C_{16}H_{23}N$: N, 6.11. Found: N, 6.09.

The secondary amine was obtained from 35 g. (0.15 mole) of the Schiff base and 22.7 g. (0.16 mole) of methyl iodide as a colorless oil in a yield of 88%, b. p. 84–85° at 8 mm., n^{20} 1.4651.

The hydrochloride, prepared by passing hydrogen chloride into an *i*-propyl ether solution of the amine, melted at 204–205° after recrystallization from a mixture of 2-propanol and *i*-propyl ether.

(12) Lindenbaum, *Ber.*, **50**, 1270 (1917).

(13) Reported b. p. 145° at 4 mm., Levene and Marker, *J. Biol. Chem.*, **97**, 563 (1932).

(14) Woodruff, Lambooy and Burt, THIS JOURNAL, **62**, 922 (1940).

Summary

1. A series of fifteen β-cyclohexylalkylamines have been prepared by catalytic hydrogenation of the corresponding phenyl analogs.
2. Four of the amines of the series were also prepared by a second method from cyclohexyl intermediates.
3. Pharmacological data for pressor activity, toxicity and central nervous system stimulation are also presented.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

Condensation of Saturated Halides with Unsaturated Compounds. IV. Condensation of *t*-Butyl Chloride with Cyclohexene[1]

BY LOUIS SCHMERLING

Previous papers in this series have described the condensation of alkyl halides with olefins[2] and haloölefins[3] in the presence of metal chloride catalysts of the Friedel–Crafts type. Extension of the reaction to a cycloölefin is discussed in the present communication.

Condensation of *t*-butyl chloride with cyclohexene yielded very little, if any, of the product (1-chloro-2-*t*-butylcyclohexane, I) to be expected by the simple addition of the alkyl group and the halogen atom to the doubly-bonded carbon atoms of the cycloölefin. Instead, the principal product was either 1-chloro-1-*t*-butylcyclohexane (II) or 1-chloro-3-*t*-butylcyclohexane (III) depending on the catalyst used. Thus, in the presence of aluminum chloride at −25 to −15°, there was obtained a 72% yield of chloro-*t*-butylcyclohexane, about 85% of which was III, the remainder being II; the principal by-product, chlorocyclohexane, was obtained in 5% yield. On the other hand, with boron fluoride as catalyst at 0°, quite pure II was produced in 23% yield together with a 15% yield of chlorocyclohexane and a 12% yield of 1-*t*-butyl-1-cyclohexene. When bismuth chloride was used at 0° or at room temperature, the chlorobutylcyclohexane (formed in 5 or in 21–25% yield, respectively) was similar to that obtained with aluminum chloride at −25 to −15°.

The composition of the product was also affected by the reaction conditions. At a lower temperature, −32 to −28°, with aluminum chloride, the proportion of III was decreased. On the other hand, by carrying out the bismuth chloride-catalyzed condensation at a higher temperature, namely, 80–97°, virtually pure III was obtained, probably because the tertiary chloride (II) which was formed was dehydrochlorinated to *t*-butylcyclohexene.

The compositions of the various chloro-*t*-butylcyclohexane products were estimated from their refractive indices and their infrared spectra. The refractive index, $n^{20}D$, of substantially pure III is 1.4685; that of II, 1.4778–1.4789.

Simons and Meunier[4] have reported that the reaction of *t*-butyl chloride with cyclohexene in the presence of hydrogen fluoride at 0 to 5° resulted in an 11% yield of 1-chloro-3-*t*-butylcyclohexane (III), an 11.5% yield of cyclohexyl fluoride, and a 65% yield of chlorocyclohexane. The structure of the chloro-*t*-butylcyclohexane was proved by showing that dehydrochlorination of the compound yielded 4-*t*-butyl-1-cyclohexene, indicating that it was either 1-chloro-3-*t*-butylcyclohexane (III) or 1-chloro-4-*t*-butylcyclohexane (IV). The *t*-butylcyclohexanol prepared from the chloride by way of the Grignard reagent yielded a 3,5-dinitrobenzoate which was not the same as the 3,5-dinitrobenzoate of 4-*t*-butylcyclohexanol obtained by hydrogenation of *p*-*t*-butylphenol. Hence, it was concluded that the chloride was not IV and that by process of elimination, it had to be III. However, this method does not take into consideration the fact that 4-*t*-butylcyclohexanol can exist in two stereoisomeric forms. It is quite possible that hydrogenation of *p*-*t*-butylphenol would yield one geometric isomer or a mixture of both isomers[5] while oxidation of the Grignard reagent of the chloride IV (which may itself be a *cis*, a *trans* compound, or a mixture) would yield the other isomer or a mixture. Therefore, the isolation of different 3,5-dinitrobenzoate derivatives can hardly be used as structural proof, particularly since 3-*t*-butylcyclohexanol was not synthesized for purposes of comparison.

The proof of structure used in the present investigation is not susceptible to the above objection. The butylcyclohexanol prepared from the chlorobutylcyclohexane was oxidized to the corresponding *t*-butylcyclohexanone which is not subject to *cis–trans* isomerism and which can, therefore, be characterized with certainty. Comparison of the semicarbazone of the unknown with the semicarbazones of authentic 2-, 3- and 4-*t*-butylcyclohexanone established the structure of the chloride as 1-chloro-3-*t*-butylcyclohexane (III).

The identity of the 1-chloro-1-*t*-butylcyclohexane (II) was indicated by the fact that it was re-

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Chicago meeting, September, 1946.
(2) L. Schmerling, THIS JOURNAL, **67**, 1152 (1945).
(3) L. Schmerling, *ibid.*, **68**, 1650, 1655 (1946).
(4) J. H. Simons and A. C. Meunier, *ibid.*, **65**, 1269 (1943).
(5) H. E. Ungnade and A. D. McLaren, *ibid.*, **66**, 118 (1944).