

2-phenylcyclohexanone and 1,2,3,4,4a,9,10,10a-octahydro-4-oxophenanthrene as starting materials.

The N-methyl- and the N,N-dimethyl derivatives of 1-phenyl-1-( $\beta$ -aminoethyl)-cyclohexane<sup>3</sup> and of 1,2,3,4,4a,9,10,10a-octahydro-4a-( $\beta$ -aminoethyl)-phenanthrene<sup>4</sup> were prepared by mono-<sup>5</sup> and dimethylation<sup>6</sup> by well known procedures.

The amines were tested for analgesic activity through the courtesy of Dr. Nathan B. Eddy, Chief Pharmacologist of the U.S. Public Health Service. We are indebted to Dr. Eddy for allowing us to publish Table I.

TABLE I

R	Analgesic effect, ED <sub>50</sub> , mg./kg.	Remarks
NH <sub>2</sub>		Not significant
NHCH <sub>3</sub>	62.9	Similar to morphine in onset (9 min.) and duration (151 min.) of effect
N(CH <sub>3</sub> ) <sub>2</sub>	24.7	Onset 9 min., duration 92 min.; less intense effect than morphine

  

R	Analgesic effect, ED <sub>50</sub> , mg./kg.	Remarks
NH <sub>2</sub>	None	Hyperactivity at 80 mg./kg. and above
NHCH <sub>3</sub>	None	Convulsant in one of 10 at 80 mg./kg.
N(CH <sub>3</sub> ) <sub>2</sub>	36.2	Onset 15 min., duration 112 min.; less intense than morphine

The phenylcyclohexanes are distinctly more effective than the phenanthrenes. In both groups, the analgesic effect is best with the dialkylamine. Preparation and testing of similar and more complex analogs are being continued.

#### Experimental

**1-Phenyl-1-( $\beta$ -methylaminoethyl)-cyclohexane.**—1-Phenylcyclohexaneethylamine hydrochloride<sup>8</sup> (2.4 g.) was dissolved in a small volume of water. The solution was basified and the free base taken up in ether. After evaporation of the ether, methyl formate (6 g.) was added and the mixture was refluxed for one hour. The excess solvent was removed and the residue was dissolved in dry ether (10 ml.). This solution was added with stirring to lithium aluminum hydride (1 g.) in dry ether (20 ml.). After refluxing of the ether had ceased, the solution was stirred at room temperature for 2 hr. Ethyl acetate was added to decompose the excess reagent. After addition of sodium hydroxide solution the clear ether solution was separated and the aqueous layer was extracted with two portions of ether. The combined ether extracts were shaken with 3 portions of 6 N hydrochloric acid (15 ml.). The combined acid extracts were evaporated to dryness *in vacuo*, the residue was basified and the free amine was again taken up in ether. The treatment with acid and evaporation were repeated. The residue was taken up in acetone; the solution deposited crystals after standing overnight. The secondary amine hydrochloride formed small colorless needles, m.p. 161–162° (acetone); the pure material weighed 0.6 g.

*Anal.* Calcd. for C<sub>13</sub>H<sub>21</sub>NCl: N, 5.5; Cl, 13.9. Found: N, 5.4; Cl, 13.9.

(3) W. E. Bachmann and E. J. Fornefeld, *THIS JOURNAL*, **73**, 51 (1951).

(4) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1524 (1953).

(5) O. Schneider and J. Hellerbach, *Helv. Chim. Acta*, **34**, 2220 (1951).

(6) *Cf. Org. Syntheses*, **25**, 89 (1945).

**1-Phenyl-1-( $\beta$ -dimethylaminoethyl)-cyclohexane.**—1-Phenylcyclohexane-ethylamine hydrochloride (4.8 g.) was dissolved in water and basified to phenolphthalein with 40% sodium hydroxide. The amine was taken up in ether and the solvent was evaporated. To the residue was added at 0°, 90% formic acid (7.8 g.) and 30% formalin (3.5 ml.). The solution was heated on the steam-bath at 90–100° for 1 hr. during which time carbon dioxide was evolved. Heating was continued for an additional 12 hr. Concentrated hydrochloric acid (10 ml.) was added and heating on the steam-bath was continued for 2 hr. and the solution was then evaporated to dryness under reduced pressure. The solid residue was crystallized from acetone-petroleum ether, then twice from acetone. The tertiary amine hydrochloride melted at 178–180° (acetone). The pure material weighed 1.2 g.

*Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>NCl: N, 5.2; Cl, 13.2. Found: N, 5.2; Cl, 13.3.

**1,2,3,4,4a,9,10,10a-Octahydro-4a-( $\beta$ -methylaminoethyl)-phenanthrene.**—The hydrochloride of this amine was prepared analogously<sup>6</sup> from 1,2,3,4,4a,9,10,10a-octahydro-4a-( $\beta$ -aminoethyl)-phenanthrene.<sup>4</sup> It formed small colorless needles, m.p. 212° (acetone).

*Anal.* Calcd. for C<sub>17</sub>H<sub>26</sub>NCl: N, 5.0; Cl, 12.7. Found: N, 4.8; Cl, 12.7.

The picrate had m.p. 162–164° (ethanol).

*Anal.* Calcd. for C<sub>23</sub>H<sub>28</sub>O<sub>7</sub>N<sub>4</sub>: N, 11.9. Found: N, 11.7.

**1,2,3,4,4a,9,10,10a-Octahydro-4a-( $\beta$ -dimethylaminoethyl)-phenanthrene.**—The hydrochloride was prepared analogously<sup>6</sup> from the corresponding primary amine. It formed colorless crystals, m.p. 207–208° (acetone-petroleum ether).

*Anal.* Calcd. for C<sub>18</sub>H<sub>28</sub>NCl: N, 4.8; Cl, 12.1. Found: N, 4.7; Cl, 12.0.

The picrate had m.p. 187–188° (ethanol). Ginsburg and Pappo<sup>4</sup> report m.p. 187–188.5° for this compound.

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#### The Cyclohexyl and Cyclopentylmethyl Radicals

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The aluminum chloride-catalyzed interconversion of cyclohexane and methylcyclopentane *via* the intermediate carbonium ions has been adequately demonstrated.<sup>2</sup> In view of the known rearrangement of the neophyl radical,<sup>3</sup> it was of interest to determine whether a similar rearrangement would occur in the cyclohexyl-cyclopentylmethyl radical system.

The di-*t*-butyl peroxide-catalyzed decompositions of cyclohexanecarboxaldehyde and cyclopentaneacetaldehyde in the liquid phase at 130 ± 5° gave as the only six-carbon atom products cyclohexane and methylcyclopentane, respectively. No evidence for rearrangement in either case was discovered, although hydrogen atom migration in the cyclopentylmethyl radical cannot be excluded.

As an example of a radical in which 1,2-hydrogen

(1) Union Oil Company, Research Center, Brea, California.

(2) H. Pines, L. Farkas Memorial Volume, Research Council of Israel, Special Publication No. 1, Jerusalem, 1952, summarizes the study of the mechanism of this isomerization.

(3) W. H. Urry and M. S. Kharasch, *THIS JOURNAL*, **66**, 1438, (1944); S. Winstein and F. H. Seubold, Jr., *ibid.*, **69**, 2916 (1947); F. H. Seubold, Jr., *ibid.*, **75**, 2532 (1953).

atom migration cannot occur, the 2,2-dimethylbutyl radical was generated by the peroxide-catalyzed decomposition of 3,3-dimethylpentanal in the liquid phase at 130°. Again only the unrearranged 2,2-dimethylbutane was isolated.<sup>4</sup> These observations provide additional examples of the stability of saturated free radicals at moderate temperatures and emphasize the special ability of the aromatic nucleus to undergo 1,2-migration in radical systems.

Support of this research by a grant from the Research Corporation is gratefully acknowledged.

#### Experimental

**Cyclohexanecarboxaldehyde.**—The acetal prepared by the interaction of cyclohexylmagnesium chloride and ethyl orthoformate was hydrolyzed by stirring with excess 10% hydrochloric acid. After ten minutes the acid was neutralized by the addition of solid sodium bicarbonate, the aldehyde was extracted with ether, and the dried extract was distilled through a 12-inch Vigreux column to yield the desired aldehyde, b.p. 36° (10 mm.),  $n_{20}^D$  1.4496.<sup>5</sup>

Decomposition of the aldehyde (6.8 g., 0.061 mole) catalyzed by di-*t*-butyl peroxide (2.9 g., 0.020 mole) for 5.5 hours at 130 ± 5° yielded 93% of the theoretical amount of carbon monoxide. Fractionation of the liquid product, including that condensed in a Dry Ice-cooled trap placed in the gas outlet line, through a Piros-Glover spinning band column at atmospheric pressure yielded no methylcyclopentane, but 0.032 mole of cyclohexane,  $n_{20}^D$  1.4260 (lit.  $n_{20}^D$  1.4262),<sup>6</sup> was isolated from its azeotrope with the *l*-

butyl alcohol produced in the peroxide decomposition. Almost identical results were obtained by decomposition of a 2 *M* solution of the aldehyde in chlorobenzene.

**Cyclopentaneacetaldehyde.**—Cyclopentaneacetic acid, prepared in 58% yield from cyclopentyl bromide and diethyl malonate, was treated with thionyl chloride to yield the acid chloride, b.p. 55° (10 mm.), amide m.p. 145.5–146.5° (lit. m.p. 143–145°<sup>7</sup>), which was hydrogenated in *p*-cymene at 65–85° over palladized barium sulfate using a sulfur-quinoline inhibitor. The aldehyde was separated as its bisulfite addition compound, which was washed with ether and decomposed by stirring with 10% aqueous sodium carbonate. Steam distillation of the mixture yielded the aldehyde, b.p. of azeotrope 94–96°, which was dried over sodium sulfate and used without further purification. The yield was 33% based on the acid chloride.

Decomposition of the aldehyde (18.4 g., 0.164 mole) catalyzed by di-*t*-butyl peroxide (7.3 g., 0.050 mole) at 132 ± 5° for 4.0 hours yielded 76% of the theoretical amount of carbon monoxide. The entire liquid product was steam distilled to a boiling point of 98°, the organic portion was taken up in toluene, washed with water to remove *l*-butyl alcohol and dried over anhydrous potassium carbonate. Fractionation of this solution through the Piros-Glover column yielded 0.070 mole of methylcyclopentane, b.p. 70° (uncor.),  $n_{20}^D$  1.4098,  $d_{25}^{25}$  0.740 (lit. b.p. 71.8°,  $n_{20}^D$  1.4097,  $d_{25}^{25}$  0.744<sup>8</sup>), as the only product of boiling point lower than that of the toluene added as solvent.

**3,3-Dimethylpentanal.**—This aldehyde, b.p. 132–135°,  $n_{20}^D$  1.4299, was prepared by the method of Schmerling.<sup>8</sup>

The peroxide-catalyzed decomposition of the aldehyde as described above gave as the only six-carbon atom product 2,2-dimethylbutane, b.p. 47° (uncor.),  $n_{20}^D$  1.3688 (lit. b.p. 49.7°,  $n_{20}^D$  1.3688<sup>8</sup>), in 75% yield based on the carbon monoxide evolved.

(7) O. Wallach and K. Fieischer, *Ann.*, **353**, 304 (1907).

(8) L. Schmerling, *This Journal*, **68**, 1650 (1946).

(4) W. H. Urry and N. Nicolaidis, *This Journal*, **74**, 5163 (1952), likewise found only 2,2-dimethylbutane as the product of the cobaltous chloride-catalyzed reaction of ethylmagnesium bromide with 1-chloro-2,2-dimethylbutane.

(5) O. Wallach and E. Isaac, *Ann.*, **347**, 331 (1906), report  $n_{20}^D$  1.4495.

(6) National Bureau of Standards, "Selected Values of Properties of Hydrocarbons," Washington, D. C., 1949.

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## Variation of the Sedimentation Coefficient with Time during a Single Velocity Ultracentrifuge Experiment<sup>1</sup>

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In the case of substances for which the sedimentation coefficient ( $s$ ) depends appreciably upon concentration ( $c$ ),  $s$  varies with time during a single ultracentrifuge experiment as a result of the progressive dilution which occurs in the plateau region of concentration in the sector-shaped cell. Since the decrease in concentration amounts to about 27% per cm. of boundary movement in the present ultracentrifuges the variation of  $s$  must be taken into account in order to utilize all of the accuracy with which velocity ultracentrifuge measurements may be made. By use of the differential equation for the ultracentrifuge,  $s$  may be expressed as a power series in time for any particular relation between  $s$  and  $c$ . Lauffer has given data for tobacco mosaic virus illustrating this effect and his data are used as a test of the theory. The calculation of the sedimentation coefficient corresponding to the concentration of the solution placed in the ultracentrifuge cell is discussed.

### Introduction

Svedberg<sup>2</sup> defined the sedimentation constant  $s$  by

$$s = \frac{dx}{dt} / \omega^2 x \quad (1)$$

where  $dx/dt$  is the velocity of transport of a component relative to the centrifuge cell,  $\omega$  is the angular velocity of the rotor and  $x$  is distance from the axis of rotation. Since  $s$  may vary considerably with concentration there are advantages in referring to

it as the sedimentation coefficient. Although the objective of a velocity ultracentrifuge experiment is to determine the rate of sedimentation of a component in the region of homogeneous solution, the actual calculations are based upon plots of refractive index gradient as a function of position in the cell. Of the several properties of the refractive index gradient curve which might be used in calculating the position of the boundary, Goldberg<sup>3,4</sup> has shown that the correct position for measuring the sedimentation coefficient of the molecules in the plateau region is given by the square root of the

(1) Presented before the Division of Physical Chemistry at the 124th Meeting of the American Chemical Society, Chicago, September 8, 1953.

(2) T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford University Press, New York, N. Y., 1940.

(3) R. J. Goldberg, *J. Phys. Chem.*, **57**, 194 (1953).

(4) See also R. Trautman and V. Schomaker, *J. Chem. Phys.*, **22**, 551 (1954).