

TABLE II

SUBSTITUTED EPINEPHRINE ANALOGS (HYDROCHLORIDES)						
X	R'	R''	M. p., °C.	Yield, %	Analyses, %	
					N calcd.	N found
Cl	H	Methyl	196-200	95	5.88	5.67
Cl	H	Ethyl	208-211	90	5.55	5.52
Cl		Methyl	202-204	97	5.00	4.85
F	H	Methyl	<sup>a</sup>	85	6.32	6.02

<sup>a</sup> This compound was obtained as a hard glass which failed to crystallize. It softened between 60-70°.

after the decomposition of the aluminum complex raised the yield of this intermediary product. 3-Chloro-4-hydroxy- $\omega$ -chloroacetophenone (0.1 mole) was added as a powder to methylbenzylamine (0.2 mole) dissolved in 500 cc. of dry dioxane. The mixture was shaken at room temperature for several hours or until crystals of methylbenzylamine hydrochloride were seen to form and then left to stand tightly stoppered for one to two days. The methylbenzylamine hydrochloride was removed by filtration on a suction flask and washed with dioxane. To the combined filtrates absolute alcohol, saturated with dry hydrogen chloride, was added, whereupon an oil was thrown out. The addition of the alcoholic hydrogen chloride was stopped as soon as the oil began to redissolve. A small quantity of dry ether was added and the mixture left in the icebox. The oil usually solidified within 24

hours. The tertiary amine hydrochloride was dissolved in methanol, refluxed for ten minutes with activated charcoal and precipitated by the addition of dry ether.<sup>22</sup> A colorless crystalline product was obtained.

1-(3-Chloro-4-hydroxyphenyl)-2-N-methylaminoethanol Hydrochloride (IV).—The substituted acetophenone (0.05 mole) prepared in the preceding step was dissolved in absolute methanol (250 cc.) A little platinum black was added as catalyst and the mixture was subjected to hydrogen at 45 lb. pressure and room temperature. The reduction was usually complete in eight to twelve hours. The catalyst was removed, the solvent evaporated under reduced pressure and the residue dried over phosphorus pentoxide in a vacuum desiccator. A hard glass formed which could be crystallized from absolute methanol by adding a sufficient amount of dry ether. The product consists of colorless crystals which are soluble in water and hot acetone as well as methanol.

### Summary

1. The preparation of a number of chlorine and fluorine containing analogs of epinephrine, synephrine and phenylethylamines has been described.

2. All of these compounds, with the exception of one which acts as a depressor, have pressor activity.

3. The toxicity of these compounds is much less than that of epinephrine.

(22) In the preparation of some of the other alkylbenzylaminoacetophenones some alkylbenzylamine came through. The hydrochlorides were subsequently separated by fractional precipitation.

CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

## Cyclopropane Derivatives. II. The Electric Moments of Some Alicyclic Compounds

BY MAX T. ROGERS AND JOHN D. ROBERTS<sup>1</sup>

There is considerable evidence that compounds in which a cyclopropane ring is located adjacent to an unsaturated linkage, such as a carbonyl group or double bond, exhibit many of the physical and chemical properties characteristic of substances containing conjugated double bonds. For example, the absorption spectrum of a double bond conjugated with a cyclopropane ring is shifted toward longer wave lengths, the shift being somewhat less than that observed for conjugated double bonds<sup>2,3,4,5</sup> and a detailed investigation of three type reactions showed that a cyclopropane ring conjugated with a carbonyl group behaved in a manner not fundamentally different from the corresponding  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>6</sup>

Since conjugation usually has a considerable effect on electric dipole moment, we have determined the electric moments of cyclopropyl chlo-

ride, cyclopropylidene chloride and cyclopropyl cyanide for comparison with those of the corresponding cyclopentyl compounds in which conjugation was expected to be unimportant. The moments of some other cyclopentyl derivatives which have not been reported previously were also determined.

### Experimental Part

#### Materials

**Benzene.**—Reagent benzene was stirred with concentrated sulfuric acid, washed with potassium hydroxide solution, then with water, and dried over calcium chloride. The material was fractionally crystallized twice, dried and distilled over sodium,  $d_{25}^{25}$ , 0.87341.

Carbon tetrachloride was purified by the method of Fieser.<sup>7</sup>

Cyclopropyl and cyclopropylidene chlorides prepared in a previous investigation<sup>8</sup> were fractionated before use: monochloride: b. p. 43°,  $n_D^{25}$  1.4079,  $d_4^{25}$  0.9899; dichloride: b. p. 75°,  $n_D^{25}$  1.4380,  $d_4^{25}$  1.2109.

Cyclopropyl cyanide was prepared by the method of Schlatter<sup>9</sup>; b. p. 65° (75 mm.),  $n_D^{25}$  1.4188,  $d_4^{25}$  0.8908.

Cyclopentyl chloride.—To a solution of 272 g. of anhydrous zinc chloride in 190 g. of concentrated hydrochloric

(1) Present address: Converse Memorial Laboratory, Harvard University, Cambridge 38, Mass.

(2) Carr and Burt, *THIS JOURNAL*, **40**, 1590 (1918).

(3) Klotz, *ibid.*, **66**, 88 (1944).

(4) Roberts and Green, *ibid.*, **68**, 214 (1946).

(5) Rogers, unpublished results.

(6) Kohler and Conant, *THIS JOURNAL*, **39**, 1404 (1917).

(7) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 365.

(8) Roberts and Dirstine, *THIS JOURNAL*, **67**, 1281 (1945).

(9) Schlatter, "Organic Syntheses," **23**, 20 (1943).

acid was added 80 g. (0.93 mole) of cyclopentanol (b. p. 139.8–140.4°). The mixture was heated on the steam-cone for an hour, cooled and the upper layer separated and washed with water, sodium bicarbonate solution, water, saturated calcium chloride solution and dried over calcium chloride. Fractionation gave 58 g. (60%) of the halide; b. p. 111–112°,  $n_D^{25}$  1.4485,  $d_4^{25}$  0.9822.

Cyclopentyl bromide was prepared by the general procedure of Noller and Dinsmore<sup>10</sup>; b. p. 58–58.5° (50 mm.),  $n_D^{25}$  1.4866,  $d_4^{25}$  1.3883.

Cyclopentyl Iodide.—A mixture of 38 g. (0.25 mole) of cyclopentyl bromide, 50 g. (0.33 mole) of sodium iodide and 200 ml. of acetone was refluxed for five hours. The solvent was distilled and the residue filtered, washed with water, sodium thiosulfate solution, water and dried over calcium chloride. Fractionation gave 35.2 g. (75%) of iodide, b. p. 65–66° (27 mm.). As the material decomposed on standing it was shaken with mercury and refractionated before use;  $n_D^{25}$  1.5457,  $d_4^{25}$  1.7462.

Cyclopentyl Cyanide.—A solution of 45 g. (0.30 mole) of cyclopentyl bromide, 30 g. (0.60 mole) of sodium cyanide and 10 g. of sodium iodide in 200 ml. of 80% alcohol was refluxed for eighteen hours, then filtered and poured into two liters of water. The organic materials were extracted with two liters of chloroform in six portions. The chloroform extract was fractionated, giving 7.6 g. (27%) of nitrile; b. p. 74.5–75° (30 mm.),  $n_D^{25}$  1.4404,  $d_4^{25}$  0.9110.

Cyclopentylidene chloride was kindly furnished by Miss Jacqueline Fergusson. This compound was prepared by the reaction of cyclopentanone with phosphorus pentachloride following the general method of Bachman and Hill<sup>11</sup>; b. p. 51° (30 mm.),  $n_D^{25}$  1.4690,  $d_4^{25}$  1.1700.

Cyclopentyl Fluoride.—To 40 g. (2 moles) of liquid anhydrous hydrogen fluoride contained in a copper reaction vessel fitted with stirrer and inlet and outlet tubes was added 58 g. (0.85 mole) of cyclopentene (b. p. 43.2°) over a period of an hour. The reaction mixture was cooled during the addition with a Dry Ice-acetone-bath. The cold mixture was forced by nitrogen pressure into a Monel beaker filled with ice. The excess hydrogen fluoride was

TABLE I  
DIELECTRIC CONSTANTS, DENSITIES AND POLARIZATIONS  
IN BENZENE AT 25°

$f_2$	$\epsilon$	$d$	$P_2$
Cyclopropyl chloride			
0.00000	(2.2725)	0.87341	( $P_1 = 26.636$ )
.00559	2.296	.87406	82.6
.01053	2.315	.87448	81.3
.01531	2.334	.87498	81.0
.02707	2.379	.87613	79.2
.05226	2.481	.87865	78.7
.09506	2.659	.88292	77.1
Cyclopropylidene chloride			
0.00683	2.311	0.87580	109.2
.01290	2.342	.87793	105.2
.02029	2.390	.88105	109.1
.03208	2.438	.88317	101.7
.03364	2.448	.88443	101.6
.05982	2.582	.89476	98.0
Cyclopropyl cyanide			
0.00605	2.392	0.87366	303.1
.01289	2.527	.87390	295.0
.02017	2.669	.87409	285.5
.02777	2.823	.87428	278.8
.03711	3.006	.87449	268.2
.04111	3.088	.87454	265.0

(10) Noller and Dinsmore, "Organic Syntheses," Coll. Vol. II, p. 358.

(11) Bachman and Hill, THIS JOURNAL, 56, 2730 (1934).

Cyclopentyl chloride			
0.00924	2.327	0.87484	116.8
.01113	2.337	.87510	114.5
.01647	2.369	.87593	115.2
.02967	2.449	.87780	115.1
.04138	2.515	.87973	113.1
Cyclopentylidene chloride			
0.00783	2.331	0.87647	144.6
.01175	2.362	.87801	145.4
.01381	2.378	.87884	145.1
.01804	2.409	.88055	143.9
.03664	2.557	.88774	143.4
.07039	2.821	.90058	139.3
Cyclopentyl bromide			
0.00747	2.325	0.87817	133.0
.01323	2.360	.88163	127.1
.01713	2.385	.88409	126.0
.03085	2.475	.89242	124.7
.04887	2.585	.90323	120.6
.08378	2.811	.92412	117.4
Cyclopentyl iodide			
0.00701	2.317	0.88102	119.2
.01281	2.350	.88718	121.0
.01679	2.374	.89142	120.8
.02250	2.410	.89742	121.5
.03161	2.465	.90694	120.4
.04720	2.559	.92326	119.0
Cyclopentyl fluoride			
0.00675	2.302	0.87381	91.4
.01653	2.344	.87420	90.8
.01895	2.359	.87429	94.2
.02285	2.376	.87447	93.4
.03805	2.446	.87512	93.4
.05074	2.503	.87559	92.2
.07136	2.597	.87653	91.1
Cyclopentyl cyanide			
0.00523	2.373	0.87375	306.1
.00759	2.418	.87399	303.6
.01359	2.531	.87432	294.6
.02071	2.665	.87480	285.9
.02804	2.811	.87514	282.3
.03953	3.037	.87576	273.2

TABLE II  
MOLAR REFRACTIONS, POLARIZATIONS AND DIPOLE  
MOMENTS

Substance	$MR_D$	$P_\infty(25^\circ)$	$\mu$ (Debye)
Cyclopropyl chloride	19.07	82.6	1.76
Cyclopropylidene chloride	24.06	109.7	2.04
Cyclopropyl cyanide	19.01	306.3	3.75
Cyclopentyl chloride	28.53	117.2	2.08
Cyclopentylidene chloride	33.09	146.4	2.35
Cyclopentyl bromide	30.86	130.0	2.20
Cyclopentyl iodide	35.53	122.8	2.06
Cyclopentyl fluoride	22.99	93.8	1.86
Cyclopentyl cyanide	27.54	309.1	3.71

carefully neutralized with 20% sodium hydroxide with occasional addition of ice to keep the mixture cold. The organic material was extracted with ether and the extract washed with water and dried over calcium chloride. After

removal of the ether the products were fractionated under reduced pressure, giving 47 g. (54%) of cyclopentyl fluoride, b. p. 49.0–49.3° (400 mm.),  $n_D^{25}$  1.3900,  $d_4^{25}$  0.9086.

#### Apparatus and Methods

The dielectric constants were measured at a frequency of 1330 kilocycles with a heterodyne beat apparatus patterned after that of Wood and Dickinson.<sup>12</sup> The standard condenser was a General Radio Type 722 Precision Condenser. The dielectric cell was similar to that described by Smyth,<sup>13</sup> having three concentric gold-plated copper cylinders insulated with mica blocks contained between concentric glass cylinders. The inlet and outlet of the cell were provided with ground joints so that the cell could be filled and emptied and the pycnometers filled in an all glass system, using compressed dry air. The total volume required was 35 ml. The pycnometers were of the graduated type described by Robertson.<sup>14</sup>

The cell was calibrated against purified benzene which was distilled in. Using 2.2725 for the dielectric constant for benzene at 25°<sup>15</sup> the replaceable capacity of the cell was found to be 130.8  $\mu\mu$  fd. The cell constant was confirmed by measuring the dielectric constant of carbon tetrachloride; the average of eight determinations (2.227) was in good agreement with the value of 2.227  $\pm$  0.001 reported by Davies.<sup>16</sup>

The dipole moments were obtained from the dielectric constants and densities of dilute solutions in benzene using the customary equations.<sup>17</sup> Values of  $P_2$  were obtained by graphical extrapolation of  $P_2$  to infinite dilution and the sum of the electronic polarization at infinite wave length and the atomic polarization was taken equal to the experimental value of the mole refraction for the sodium D line,  $MR_D$ . The data are given in Tables I and II.

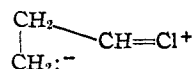
#### Discussion of Results

Although electric moments calculated from dielectric constant measurements made on substances in the vapor state are more reliable than values obtained in solution, relative moments obtained using the same solvent under similar conditions appear to be closely comparable to the corresponding relative values from determinations on the vapor. All values quoted for comparison in this paper, unless otherwise stated, are those obtained in dilute solutions in benzene at 25° and are given in Debye units.

The dipole moment of cyclopropyl chloride<sup>18</sup> is 0.3D lower than cyclopentyl chloride and 0.28D lower than the value 2.04D reported for isopropyl chloride.<sup>19</sup> Consideration of induction effects alone in cyclopropyl chloride would lead to the conclusion that the moment should be as large or larger than that of cyclopentyl chloride since the polarizable matter is concentrated more nearly in the line of the original dipole due to the small  $\angle$ C–C–C. The difference in moments induced in the hydrocarbon portion of the molecule due to the difference in polarizabilities should be no

more than between isopropyl chloride and 3-chloroheptane,<sup>20</sup> for which identical moments have been reported. It seems, therefore, that some additional effect must operate which tends to lower the moment.

The ionic resonance form  $\overset{\ominus}{\text{C}}\text{H}_2\text{—CH=Cl}^+$  (I) contributes sufficiently to the structure of vinyl chloride to make the electric moment 0.6D (measured in the vapor) lower than ethyl chloride.<sup>21</sup> The extent of the contribution of I calculated from the bond lengths is about 15%<sup>22</sup> and from the electric moment data about 7%.<sup>21</sup> For cyclopropyl chloride (or any other saturated alicyclic chloride) it is possible to write two equivalent ionic structures (II) analogous to I and, if we



assume the separation of charge to be roughly the same for I and II, a 2–3% contribution of II to the hybrid of cyclopropyl chloride would account for the observed moment. It is not unreasonable to expect a significant contribution of II to the structure of cyclopropyl chloride because the carbon–carbon bond energy in cyclopropane is probably lower than for normal bonds. Thus, if the "strain" energy (25 kcal.) is considered to be divided among the three carbon–carbon bonds, assuming the carbon–hydrogen bond energies normal, then the C–C bond energy would be about 50 kcal./mole in cyclopropane. This value of the C–C bond energy is close to the value calculated<sup>23</sup> assuming that the decrease in bond energy is due to smaller overlapping of the tetrahedral bond orbitals when the bond angle is decreased to 60° (the C–H bond energies being considered as essentially unchanged). On this basis the contribution of II to the structure of cyclopropyl chloride will not be so great as that of I to vinyl chloride because II will have about 8 kcal. of additional instability resulting from the difference between the energy of a cyclopropane ring bond (50 kcal.) and the 42 kcal. gained by making a double from a single bond in I. Despite this additional instability of ionic structures of cyclopropyl chloride it is possible that they might contribute enough to account for the observed moment and, in any event, structures such as II should certainly be more important in cyclopropyl than in cyclopentyl or cyclohexyl chlorides where the strain energies of the rings are negligible. In this treatment we have neglected the effects of contributions of resonance forms of

the type  $\overset{\text{H}}{\text{C}}\text{—C}^{\ominus}$  as presumably there will be little

(12) Wood and Dickinson, *THIS JOURNAL*, **61**, 3259 (1939).

(13) Smyth and Morgan, *ibid.*, **50**, 1547 (1928).

(14) Robertson, *Ind. Eng. Chem., Anal. Ed.*, **11**, 464 (1939).

(15) Hartshorn and Oliver, *Proc. Roy. Soc. London*, **A123**, 664 (1929).

(16) Davies, *Phil. Mag.*, **21**, 1 (1936).

(17) Smyth, "Dielectric Constants and Molecular Structure," The Chemical Catalog Co., New York, N. Y., 1931, Chap. I.

(18) ADDED IN PROOF.—After the present paper was accepted for publication a paper by Spinrad (*THIS JOURNAL*, **68**, 617 (1946)) appeared in which  $\mu$  for cyclopropyl chloride was reported to be 1.78 D in excellent agreement with the value obtained by us.

(19) Parts, *Z. physik. Chem.*, **B13**, 312 (1931).

(20) Errera and Sherrill, *THIS JOURNAL*, **52**, 1993 (1930).

(21) Hugill, Coop and Sutton, *Trans. Faraday Soc.*, **34**, 1518 (1938).

(22) Pauling, "The Nature of the Chemical Bond," 2nd ed., The Cornell University Press, Ithaca, N. Y., 1940, p. 216.

(23) Skinner, *Trans. Faraday Soc.*, **41**, 645 (1945).

difference between cyclopentyl and cyclopropyl halides on this score.

The moment observed for cyclopropylidene chloride is about 0.3D below that for cyclopentylidene chloride and 0.2D below that for isopropylidene chloride.<sup>24</sup> This indicates again that there may be a small contribution in the cyclopropyl compound from structures placing a positive charge on the chlorine atoms. The moments observed for vinylidene chloride,<sup>25</sup> 1.18D, and 1,1-dichloropropene-1,<sup>23</sup> 1.73D, are 1.0D and 0.45D, respectively, lower than isopropylidene chloride. It is interesting to note that the moments of cyclopropylidene, cyclopentylidene and isopropylidene chlorides are larger than the respective monochlorides although one might expect the reverse to be true from the relative magnitudes of the moments of the methylene and methyl halides.

The moment of cyclopropyl cyanide, 3.75D, is 0.04D higher than cyclopentyl cyanide and 0.14D higher than isopropyl cyanide.<sup>5</sup> This may indicate a small contribution from structures  $\text{CH}_2\text{---CH=C=N:}^-$   $\begin{matrix} | \\ \text{CH}_2^+ \end{matrix}$  tending to increase the moment, just as in benzonitrile, which shows an increase of about 0.25D due to conjugation. However, it must be observed that no great confidence can be placed in the interpretation of these moments since vinyl cyanide shows a decrease of about 0.1 to 0.2D below the aliphatic cyanides both in vapor<sup>26</sup> and solution.<sup>5</sup> The increase might be due entirely, or in part, to effects of induction.

(24) Gross, *Physik. Z.*, **32**, 587 (1931); **33**, 719 (1932).

(25) Errera, *ibid.*, **27**, 764 (1926).

(26) Hurdis and Smyth, *THIS JOURNAL*, **65**, 89 (1943).

A comparison of the cyclopentyl compounds with the corresponding *s*-butyl or isopropyl derivatives indicates that the observed moments are normal. Thus, in benzene solution the moment observed for *s*-butyl chloride is 2.09<sup>27</sup>; for *s*-butyl bromide, 2.12<sup>27</sup>; for *s*-butyl iodide, 2.04<sup>27</sup>; for isopropylidene chloride, 2.18<sup>24</sup>; and for isopropyl cyanide, 3.61.<sup>5</sup> The greater polarizability of the cyclopentane ring, and the fact that a larger portion of polarizable matter is held near to the line of the original dipole, would tend to make the contribution from induced dipoles larger in the cyclopentyl compounds and so the observed moments should be slightly larger and indeed small increases are occasionally observed. The moment of cyclopentyl fluoride is the first value to be reported for a secondary fluoride and, as would be anticipated, falls between those observed for *n*-amyl and *t*-amyl fluorides.<sup>5</sup>

### Summary

The dipole moments of cyclopropyl chloride and 1,1-dichlorocyclopropane in benzene solution have been shown to be about 0.3D less than the corresponding cyclopentyl compounds. This has been interpreted as indicating a small contribution from ionic resonance structures analogous to the principal ionic resonance structures in vinyl chloride and chlorobenzene.

The dipole moments of the cyclopentyl halides and cyanide are close to those of the corresponding secondary aliphatic compounds.

(27) Parts, *Z. physik. Chem.*, **B7**, 327 (1930).

LOS ANGELES 24, CALIF.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE WM. S. MERRELL CO.]

## The Alkaline Hydrolysis of Fluorenone-spirohydantoin

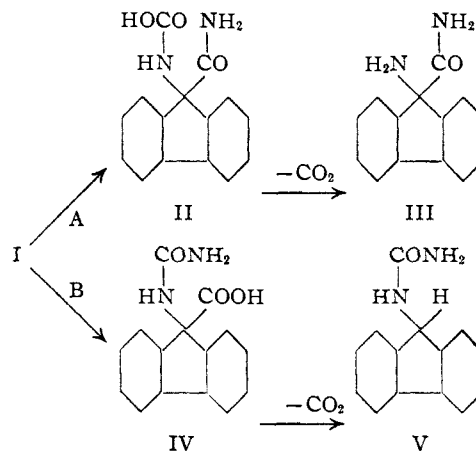
By G. H. HARRIS,<sup>1</sup> B. R. HARRIMAN<sup>2</sup> AND KEITH W. WHEELER

Mild hydrolysis of fluorenone-spirohydantoin (I) might be expected to proceed along one of two possible courses, as A or B, below. There are numerous cases reported in the literature<sup>3</sup> in which hydrolysis of other hydantoins in the presence of barium hydroxide leads to substituted hydantoin acids. In these cases the hydrolysis follows course B and compounds of the type illustrated by (IV) are isolated. In other cases wherein hydrolysis leads to an amine, the same product would result from either course.

(1) Present address: The Paraffine Companies, Inc., San Francisco, Calif.

(2) Present address: Ansco, Binghamton, New York.

(3) Baeyer, *Ann.*, **130**, 160 (1864); Bailey, *Am. Chem. J.*, **28**, 395 (1902); Biltz and Heyn, *Ber.*, **45**, 1672 (1912); Heintz, *Ann.*, **169**, 128 (1873); Klason, *Chem. Ztg.*, **14**, 200 (1891); Pinner, *Ber.*, **21**, 2321 (1888); Pinner and Spilker, *ibid.*, **22**, 687 (1889); Urech, *Ann.*, **164**, 264 (1872); West, *J. Biol. Chem.*, **34**, 191 (1918); Wheeler and Hoffman, *Am. Chem. J.*, **45**, 373 (1911).



It has been reported<sup>4</sup> that hydrolysis of fluorenone-

(4) McCown and Henze, *THIS JOURNAL*, **64**, 689 (1942).