m. p. 53-55°. Crystallization from 90% methanol raised the m. p. to 61-62.5°. A 2,4-dinitrophenylhydrazone was obtained, m. p. 180°.[5]

***p*-Acetylaniline.**—Fifty-four grams (0.4 mole) of acetanilide and 50 ml. of acetic anhydride were refluxed with 4 g. of iodine, distilling the acetic acid formed through a 38-cm. Vigreux column. In fifteen minutes, 30 ml. of distillate was collected, b. p. 110-120°. An additional 25 ml. of acetic anhydride was added to the reaction mixture and 25 ml. of distillate collected, the final vapor temperature rising to 132°. The reaction mass was poured into 250 ml. of water, the oil extracted twice with 75-ml. portions of ethylene dichloride and the excess iodine washed out with bisulfite. Removal of the solvent left a tarry residue which was hydrolyzed by refluxing for one hour with 50 ml. of concentrated hydrochloric acid. After being made strongly alkaline, the unreacted aniline was steam distilled and the residual black tar extracted twice with 75-ml. portions of ethylene dichloride, washed until neutral and dried over sodium sulfate. The solvent was removed and the residue distilled, yielding 10.5 g. (19.4%) of a golden yellow oil, b. p. 165-168° (6 mm.), which solidified, m. p. 67-68°. Crystallization from hot water gave white crystalline *p*-acetylaniline, m. p. 105-106°; acetyl derivative, m. p. 165-166°.[6]

Refluxing the reactants for two hours without removal of the acetic acid formed reduced the yield of *p*-acetylaniline to 7%.

**α-Phenyl Naphthyl Ketone.**—Twenty-five and six-tenths g. (0.2 mole) of naphthalene was refluxed gently with 28 g. (0.2 mole) of benzoyl chloride in the presence of 4 g. of iodine. A vigorous evolution of hydrogen chloride began immediately and ceased within two hours. The reaction mass was taken up in 150 ml. of ethylene dichloride, washed with dilute sodium hydroxide and bisulfite and the solvent and unreacted naphthalene removed by steam distillation. The black, tarry mass was extracted with benzene, washed with water and dried over sodium sulfate. The solvent was removed and the residue distilled, yielding 23.9 g. (51.7%) of a golden yellow, viscous liquid, b. p. 165-169° (1 mm.) which slowly solidified, m. p. 73-74°. The product was crystallized from ethanol, m. p. 74-75°, and gave an oxime, m. p. 161°.[7] One gram of the crude ketone dissolved in 20 ml. of benzene containing 1 g. of picric acid deposited, after fourteen days at 5°, 100 mg. of the picrate of the β-isomer, m. p. 112-113°, equivalent to 5% of β-benzoylnaphthalene.[3]

## Summary

Acylations have been carried out successfully on the more active members of the benzene series, using iodine as a catalyst.

Harrison, New Jersey Received December 20, 1947

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(5) Ferrante and Bloom, *Am. J. Pharm.*, **105**, 383 (1933), report m. p. of 180°.

(6) Kunckell, *Ber.*, **33**, 2641 (1900), report m. p. of 166-167°.

(7) Betti and Poccianti, *Gazz. chim. ital.*, **45**, I, 374 (1915), list m. p. of 161°.

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[Contribution from the University of Chicago Toxicity Laboratory]

# The Volatility and Vapor Pressure of Ten Substituted 2-Chloroethylamines[1]

By C. Ernst Redemann,[2] Saul W. Chaikin and Ralph B. Fearing[3]

In a study of the toxicity and vesicancy of the so-called nitrogen mustards it soon became apparent that neither the necessary volatility nor vapor pressure data for assessing these agents were available. The first member of this group of 2-chloroethylamines to be prepared, and its potent vesicant action described, was tris-(2-chloroethyl)-amine.[4] However, no vapor pressure data were given nor were any subsequently reported. It was, therefore, necessary to measure the volatility before any quantitative evaluation of these compounds could be made. In the course of this study the volatility and vapor pressure were determined for ten substituted 2-chloroethylamines at temperatures between 0 and 60°. Their numerical values are reported here.

The method employed for measuring the volatility and the equations by which the vapor pressure was calculated from the volatility have been described in two earlier reports.[5] The equations derived for these compounds should not be used at temperatures much outside the specified range without recognizing that the values so computed may have errors considerably larger than the probable error over the 0 to 60° interval.

## Experimental

The details of the measurements and the apparatus have been given in earlier reports.[5]

All the compounds employed in this study were prepared in laboratories other than that of the authors. The source of each compound is given in Table I. All but one of the 2-chloroethylamines were received as the hydrochlorides, well crystallized compounds of definite, reproducible melting point, which could be readily purified by crystallization from suitable solvents. These hydrochlorides were usually received in an analytically pure form and were stored in a cool, dry place until they were used. Each hydrochloride was converted into the free base by treatment with a cold 50% aqueous solution of potassium hydroxide. Where practical the base was separated from the aqueous solution without use of any solvent; when the amine phase would not separate cleanly from the aqueous phase the former was diluted with ethyl ether before separation. The amines were dried over anhydrous potassium carbonate before distillation. The dry amine was distilled under reduced pressure, the pressure being so chosen that the amine boiled below 100° in all but two cases (see Table I). For eight of the ten amines the boiling point was constant; for *t*-butyl-bis-(2-chloroethyl)-amine a one degree boiling range was tolerated, and for 4-(2-chloroethyl)-morpholine the sample submitted was too small to purify before use and was therefore run as received.

Since these amines slowly give self-condensation products, especially when not completely dry, they were placed in the vaporizer immediately after distillation and

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(1) This work was carried out under contract with the National Defense Research Committee of the Office of Scientific Research and Development.

(2) Present address: 770 S. Arroyo Parkway, Pasadena 2, Calif.

(3) Present address: 622 N. East Ave., Oak Park, Ill.

(4) Ward, This Journal, **57**, 914 (1935).

(5) (a) Bent and Francel, *ibid.*, **70**, 634 (1948); (b) Redemann, Chaikin and Fearing, *ibid.*, **70**, 631 (1948).

TABLE I

CONSTANTS OF THE SAMPLES OF THE TEN 2-CHLOROETHYLAMINES USED AND PRECISION OF DATA

| Amine | Boiling point °C. | Boiling point Mm. | Refractive index, $n_D$ | Density G./cc. | Density °C. | $A$ | Constants $A'$ | $B$ | Percentage deviation from smoothed curve of points calcd. from least sq. equation Maximum | Percentage deviation from smoothed curve of points calcd. from least sq. equation Mean | $L_{ev}$, Cal./mole |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R—N$(C_2H_4Cl)_2$ | | | | | | | | | | | |
| Ethyl[a] | 85.5 | 12 | 1.4653[d] | 1.0861 | 23 | 9.01892 | 12.45482 | 2868.9 | 1.71 | 0.97 | 13,100 |
| *n*-Propyl[a] | 96 | 10 | | 1.05929 | 23.3 | 9.01884 | 12.47955 | 2966.7 | 1.76 | .56 | 13,600 |
| *n*-Butyl[a] | 106.3 | 9 | | 1.0365 | 25 | 9.28361 | 12.78578 | 3169.8 | 2.7 | .57 | 14,500 |
| Isobutyl[a] | 79 | 2 | | 1.0328 | 20 | 9.42242 | 12.92461 | 3152.5 | 0.22 | .17 | 14,400 |
| *s*-Butyl[a] | 100 | 7.5 | | 1.0455 | 25 | 9.16684 | 12.66901 | 3109.5 | .42 | .16 | 14,200 |
| *t*-Butyl[a] | 71–72 | 2 | | 1.0484 | 22 | 9.13430 | 12.63649 | 3050.9 | .26 | .11 | 14,000 |
| Cyclohexyl[a] | 103[c] | 1 | 1.4944[d] | 1.0964 | 21 | 8.60897 | 12.16478 | 3258.8 | .49 | .28 | 15,000 |
| 2-Chloroethyl[a] | 94 | 1 | 1.4925[e] | 1.2093 | 25 | 9.41621 | 12.92221 | 3393.4 | .54 | .31 | 15,500 |
| 4-(2-Chloroethyl) morpholine[b] | | | | 1.1062 | 22 | 8.91971 | 12.29993 | 2808.7 | 1.59 | 1.48 | 12,900 |
| bis-(2-Chloropropyl) methylamine[a] | 56 | 2 | 1.458[f] | 1.0381 | 21.5 | 8.99698 | 12.46728 | 2850.4 | 2.70 | 1.74 | 13,000 |

[a] Prepared in the laboratory of Dr. G. H. Coleman. [b] Supplied by Dr. M. S. Kharasch. Quantity too small for further purification. Fifteen per cent. had to be evaporated before a constant volatility was reached. [c] Melting point, −3°. [d] 25°. [e] 25.2°. [f] 21°.

were run as promptly as feasible. When there was evidence of self-condensation having occurred during a determination, as shown by the separation of a solid quaternary ammonium salt (see Discussion), the vaporizer unit was cleaned and filled with freshly distilled amine before continuing the measurements.

Dry nitrogen was used as the entrainment gas to avoid possible oxidation of the compounds. The values for the boiling point, refractive index and density of the samples of the compounds studied are given in Table I.

## Discussion

This series of compounds presented certain difficulties which were not encountered in our previous studies.[5b,6] The chlorine atom in the $\beta$-position to the amino group, while not highly reactive, still shows sufficient activity to react slowly at room temperature with the amino group in an adjacent molecule. Since the amines studied in this series are all tertiary amines, reaction with the $\beta$-halogen of an adjacent molecule leads to the production of a quaternary ammonium compound. In these cases the quaternary ammonium chlorides are very sparingly soluble and were observed to crystallize from the reaction mixture. The insolubility of the salts was helpful for two reasons, first, it served as an index of the amount of polymerization which had taken place and, second, the solubility proved to be so low that it did not alter the vapor pressure measurably, as shown by the fact that volatilities measured for samples free from polymer agreed within experimental error with volatilities measured upon samples with some crystalline polymer. Nevertheless, a vigorous effort was made to make measurements only upon samples free from any solid polymer.

It was also observed that much longer time of contact was necessary in order to produce equilibrium between the liquid and its vapor with this group of compounds than was found for any other group of compounds studied. Consequently, for most of these runs the rate of flow of the nitrogen through the saturator was reduced 50 to 75% over the values used for other compounds of similar boiling point.

In Table I are recorded, in addition to the previously mentioned properties, the three constants $A$, $A'$, and $B$ for the equations

$$\log p = A - B/T \qquad (1)$$
$$\log WT = A' - B/T \qquad (2)$$

computed by the method of least squares from the experimental points and also the percentage deviation from the smoothed curve of the points calculated from the least squares equation. The constants apply when the pressure, $p$, is expressed in millimeters of mercury, the temperature, $T$, is the centigrade temperature plus 273.2 and the volatility, $W$, is expressed in milligrams of agent per liter of air (or nitrogen). An average value for the molar heat of evaporation, $L_{ev}$, in calories per mole over the temperature range 0 to 60° is also given for each compound. These values were calculated from equation (1).

The mean percentage deviation of the *experimental* points from the smoothed curve is under 2% for all compounds except cyclohexyl-*bis*-(2-chloroethyl)-amine which has a mean deviation of 5.4%. This arises from the very small volatility of this compound, since the amine collected for weighing was only about 5 mg. at the lowest temperature.

**Acknowledgment.**—Thanks are due to Miss Dora Benedict for her helpful work in making some of these measurements.

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(6) Redemann, Chaikin, Fearing and Benedict, THIS JOURNAL, **70**, 637 (1948).

## Summary

1. The volatility of ten substituted 2-chloroethylamines has been measured between 0 and 60° by an air saturation method.
2. From the measured volatilities vapor pressures have been calculated. Logarithmic equations have been developed for both the vapor pressure and the volatility as a function of the temperature.
3. The mean molar latent heat of evaporation over the temperature range 0 to 60° has been computed from the vapor pressure equation for each compound.

CHICAGO 37, ILLINOIS RECEIVED DECEMBER 5, 1947

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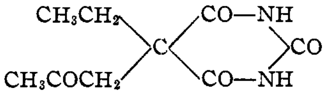
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

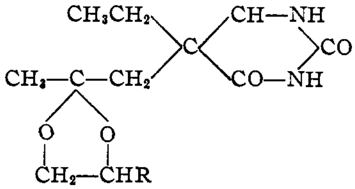
# Cyclic Acetals Related to Ethylacetonylbarbituric Acid

BY CHARLES D. HURD AND MARGARET L. MCAULEY

This investigation deals with the synthesis and reactions of certain new derivatives of ethylacetonylbarbituric acid (I). This acid was synthesized from sodium ethylbarbiturate and chloroacetone, instead of the previously used[1] bromoacetone. To use chloroacetone, it was found that sodium iodide was an effective catalyst.[2] Yields of 75% of I were obtained with this catalyst as contrasted with 10-32% yields without it. Butylacetonylbarbituric acid was similarly prepared and with the same high yield. In view of this, it is of interest to note that no significant reaction product could be obtained when solutions of sodium ethylbarbiturate, 2-chloromethyl-2-methyldioxolane (made from chloroacetone and ethylene glycol), and sodium iodide were mixed and treated similarly. Ethyl *sodio*-butylmalonate also failed to give a reaction product with 2-chloromethyl-2-methyldioxolane at refluxing temperature in alcohol solution.



(I)

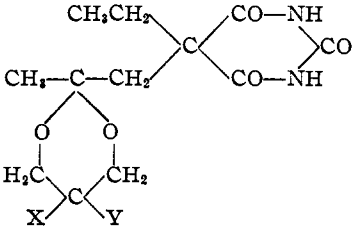


II, R = H

III, R = $CH_3$

Dioxolanes of the structure II or III were synthesized by reaction of ethylacetonylbarbituric acid with ethylene glycol or propylene glycol in the presence of *p*-toluenesulfonic acid. The water formed in the reaction was removed as formed by slowly distilling benzene or toluene from the reaction mixture. The compounds formed were high melting, crystalline solids.

1,3-Dioxanes represented by formula IV, V were synthesized similarly from I by reaction with trimethylene glycol or tris-(hydroxymethyl)-nitromethane. These compounds all melt above 200°. Conditions were not found for satisfactory interaction of (I) and 2-nitro-2-methyl-1,3-propanediol.



IV ($X = Y = H$)

V ($X = NO_2$, $Y = CH_2OH$)

VI ($X = NH_2$, $Y = CH_2OH$)

VII ($X = NHAc$, $Y = CH_2OH$)

The nitro group in 5-ethyl-5-(1-methyl-4-nitro-4-hydroxymethyl-2,6-dioxacyclohexyl)-methylbarbituric acid (V) was readily reduced at 100° to an amino group under a hydrogen pressure of 1600 lb./sq. in., using Raney nickel catalyst The amine (VI) is moderately soluble in water· In accordance with its dipolar ion character, it is insoluble in non-polar solvents. Conditions were not found for the acetylation of this amine by acetic anhydride, but acetylation to VII was achieved readily by the use of ketene.

We are indebted to Edgar B. Carter, Lucy Johnson and G. M. Everett of Abbott Laboratories for pharmacological tests made on the above compounds. These compounds were tested: II, III, IV, butylacetonylbarbituric acid (VIII), and acetonylbarbituric acid (IX). The compounds were non-toxic toward mice by intravenous injection in doses of 50 to 200 mg./kg., but such doses produced no hypnotic effect. To test anticonvulsant activity, mice were given 400 mg./kg. orally and after various periods of time were tested with 100 mg./kg. of metrazol with results shown in Table I.

It is seen that all except IX show some anticonvulsant action. Compound III was tested further with oral doses of 500 mg./kg. After periods of 10, 30, 60, 120 minutes, 100 mg./kg. of metrazol was given. All mice showed jerks and approximately half showed convulsions after all

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(1) (a) Kirsanov and Ivashchenko, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1576 (1938); (b) Dox and Houston, THIS JOURNAL, **46**, 252 (1924).

(2) Hurd and Perletz, *ibid.*, **68**, 38 (1946).