NOTES

Specific Heats of Acetaldehyde and Acetaldehyde Dibutyl Acetal

By Albert Z. Conner, Philip J. Elving[1] and Samuel Steingiser[2]

In studying the reaction

$$CH_3CHO + 2C_4H_9OH = CH_3CH(OC_4H_9)_2 + H_2O$$

it was necessary to know the specific heats of the compounds involved at various temperatures. Although values for water[3] and *n*-butanol[4] can be found in the literature, no values for the specific heats of liquid acetaldehyde or of acetaldehyde dibutyl acetal could be found. Accordingly, the specific heats of the latter two compounds were measured on redistilled samples of acetaldehyde (boiling at 20° at 760 mm. of mercury) and of acetaldehyde dibutyl acetal (boiling at 90° at 30 mm.); the purity of the two compounds based on physical constants and chemical analysis was not less than 99 mole per cent.

A calorimeter, similar to that described in Weissberger,[5] was employed, consisting of a silvered Dewar flask closed by a stopper through which were introduced a Beckmann thermometer, an ordinary mercury thermometer, a propeller stirrer, and a manganin coil heater. The calorimeter was almost completely immersed in a bath capable of maintaining the temperature within ±1° of the temperature of the calorimeter. The heat input was measured electrically as described in Weissberger,[6] and the time was measured by means of a stop watch.

The duration of the run was chosen to give approximately a one-degree rise in temperature. For ease of calculation and uniformity of conditions, two-minute runs were used in the determinations on both of the compounds. This time was of necessity increased to three minutes when water was used in the calibration of the calorimeter.

Due to the extremely small thermal head between calorimeter and bath, the conduction, convection and radiation losses were assumed to be negligible. In order, however, to correct for possible evaporation losses and to determine which portion of the heat input was utilized in the resultant temperature rise, a plot of calorimeter temperature *versus* time was made for each run. The corrected temperature rise was then obtained by the linear extrapolation of the temperature observations which constituted the "fore" and "after" periods, to the time when the temperature of the calorimeter was equal to the average of the values at the start and finish of the reaction period.[7]

The average values of the specific heats obtained by the method described are as follows

Compound	Temp., °C.	Specific heat, C_p cal./g.-degree
Acetaldehyde	0	0.522 ± 0.004
Acetaldehyde dibutyl acetal	25	.483 ± .004
	40	.484 ± .004
	60	.498 ± .005
	80	.513 ± .005

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[3] N. H. Osborne, H. F. Stimson and D. C. Ginnings, *J. Research Natl. Bur. Standards*, **23**, 238 (1939).

[4] E. W. Washburn, ed., "International Critical Tables," Vol. 5, McGraw-Hill Co., New York, N. Y., 1929, p. 108.

[5] A. Weissberger, ed., "Physical Methods of Organic Chemistry," Vol. 1, Interscience Publishing Co., New York, N. Y., 1945, p. 365.

[6] Ref. 3, p. 330–332.

[7] Ref. 3, pp. 337–340.

Recognition of Solid Solutions

By J. G. Aston, M. R. Cines and H. L. Fink

It has not generally been recognized that a complication of solid solution formation during determination of the amount of impurity by a study of melting point can frequently be detected from calorimetric melting point data on a single sample of a compound.

In the evaluation of the purity of samples used in calorimetric third law studies, Johnston and Giauque[1] pointed out that there were two ways in which the impurity might be determined. First, it is possible to determine purity from the melting point depression. Second, purity may be calculated from "premelting heat capacity." When the impurity is ideally liquid-soluble and solid-insoluble, the results of calculation by the two methods should agree. In fact, when the amount of impurity calculated from melting point depressions and from premelting heat capacities agree it may be considered as sufficient proof of the ideality of the solutions and the solid insolubility of the impurity.

A consideration of the shape of the heat–capacity–temperature curve for an ideal homogeneous solid solution near the fusion region shows that the heat capacity will break sharply at the beginning of fusion (solidus point) rather than gradually increase as in the case where no solid solution forms and the composition is far removed from that of the eutectic. Therefore, when solid solutions are studied calorimetrically in the fusion region, it will be found that the mole per cent. of impurity calculated from "premelting" heat ca-

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[1] Johnston and Giauque, This Journal, **51**, 3194 (1929).

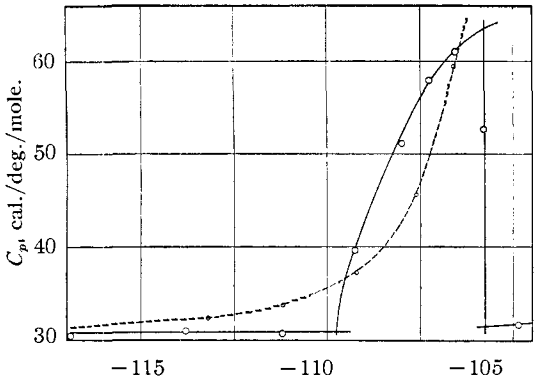

Fig. 1.—Heat capacity of 2,2-dimethylbutane with 4.6 mole per cent. 2,3-dimethylbutane added.

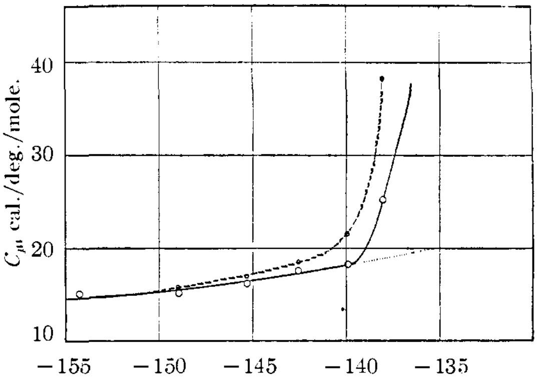

Fig. 2.—Heat capacity of butadiene-1,2.

pacities will be much less than those found by melting point depression.

As an example of the behavior of a solid solution, the following results were obtained from the calorimetric data obtained on a mixture of 95.4 mole per cent. 2,2-dimethylbutane and 4.6 mole per cent. 2,3-dimethylbutane (a system known to form solid solutions)[2a] in a specially designed melting point calorimeter for which an accuracy of 2-3% is claimed.[2b] The amount of 2,3-dimethylbutane in the mixture was calculated to be 0.24 mole per cent. based on the 50 and 100 per cent. melted points. It was not possible to calculate the amount of impurity from the "premelting" heat capacities as there was no "premelting" rise in the heat capacity curve but rather a sharp break indicative of solid solutions. This sharp break can be seen in Fig. 1 in which heat capacity determinations on this mixture over the temperature range where it changes completely from solid to liquid are plotted as the solid line. The dashed curve represents the "premelting" heat capacity curve which was calculated for 0.24 mole per cent. liquid-soluble solid-insoluble impurity. The dashed curve was obtained by adding to the molal heat capacity of the sample, as determined at the same time as the melting point, the excess heat capacity which would be caused by "premelting" of the sample were it to contain 0.24 mole per cent. solid-insoluble impurity.

As a second example, the following results were obtained in a calorimetric determination of the purity of a sample of butadiene-1,2. Purity calculated from the 50 and 100% melted points was 99.87 and from the premelting heat capacities was 99.95 which indicates the presence of solid soluble material. The heat capacity data are plotted in Fig. 2 in which the dotted curve represents an attempted extrapolation to obtain the heat capacity curve if no premelting occurred, while the dashed curve represents the heat capacities calculated on the basis of 0.13 mole per cent. liquid-soluble solid-insoluble impurity.

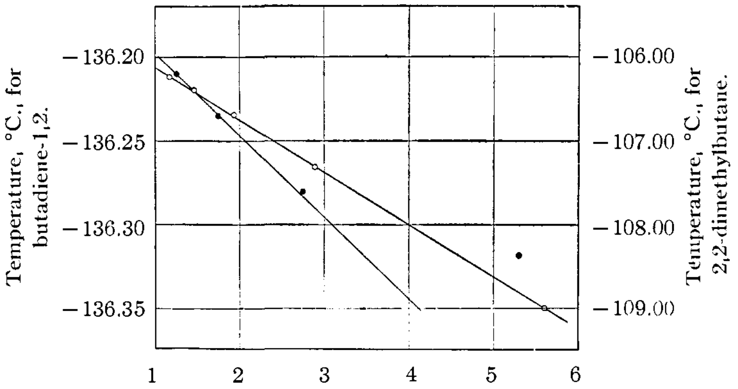

Fig. 3.—Melting curves for butadiene-1,2 (○) and 2,2-dimethylbutane (●).

In Fig. 3 the equilibrium temperatures during melting are plotted against the reciprocal of the fractions melted. The straight lines are the theoretical curves obtained for the molar impurities as calculated from the 50 and 100% melted points; the solid points are the data for the 2,2-dimethylbutane–2,3-dimethylbutane mixture and the open circles are the data on 1,2-butadiene. It can be seen that the deviation of the points from the lines are not as spectacular as are the differences between the purities calculated from the "premelting" heat capacities and the melting point depression.

Thus, it is clear that by an examination of the "premelting" heat capacities and by a comparison with the values to be expected on the basis of the impurity determined from melting point depression it is possible by calorimetric data to reveal the existence of solid-soluble impurities. We

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(2) (a) Fink, Cines, Frey and Aston, THIS JOURNAL, **69**, 1501 (1947); (b) Aston, Tooke, Fink and Cines, *Ind. Eng. Chem., Anal. Ed.*, **19**, 218 (1947).

hasten to add that the foregoing statement applies only for systems containing relatively small amounts of the second component which would be likely to behave as an ideal solute because of its small concentration and chemical similarity, for example, hydrocarbons containing a small amount of a second component as impurity.

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The Resolution of Atabrine Dihydrochloride

BY F. A. BACHER, R. P. BUHS, J. C. HETRICK,[1] W. REISS[2] AND N. R. TRENNER

In a forthcoming publication Seeler and Malanga[3] describe their findings concerning the comparative activity of the optical isomers of atabrine against avian malaria. In our attempt to prepare the necessary optical isomers used in the above work, the methods of Chelintsev and Osetrova[4] were tried without marked success. As a result we investigated the use of other bromocamphorsulfonic acids and, as will be described below, found that the 3-bromo-[*d*-camphor]-sulfonic acid-7 formed diastereoisomeric salts which were easily separable.

Experimental

3-Bromo-(*d*-camphor)-sulfonic Acid-7.—This substance was prepared using the method of Kipping and Pope,[5] who described the formation of its ammonium salt. The actual free acid was prepared from the ammonium salt by the use of excess barium hydroxide to eliminate the ammonia followed by quantitative addition of 2 *N* sulfuric acid to remove the barium as sulfate. The aqueous solution of the free acid so obtained was concentrated under reduced pressure to a light yellow sirup which crystallized as a hydrate. This was subsequently dried *in vacuo* at 100° to yield the solid anhydrous acid which was not further treated before use.

The Resolution of *d,l*-Atabrine.—Eleven and four-tenths grams of atabrine base and 17.6 g. of 3-bromo-(*d*-camphor)-sulfonic acid-7 were heated on the steam-bath in 10 cc. of ethylene glycol monoethyl ether (cellosolve) until a clear thick sirup was obtained. The sirup was then dissolved in 500 cc. of hot acetone, immediately filtered and the filtrate allowed to stand at room temperature at least overnight, during which time crystallization occurred. Nine grams (fraction 1) of a partially resolved *d*-atabrine 3-bromo-(*d*-camphor)-sulfonate-7 was obtained on filtering.

In following the degree of resolution achieved in any fraction, the following procedure was developed for evaluating the specific rotation. A weighed sample of the atabrine sulfonate salt (about 20 mg.) was dissolved in about 10 cc. of water and after treatment with 2 drops of about 30% sodium hydroxide, to liberate the atabrine base, the whole was extracted with an equal volume of diethyl ether. After equilibration and washing with water, an aliquot of the ether phase (8 cc.) was removed and extracted with 3 cc. of water containing 2 drops of *N* hydrochloric acid. The ether phase was then removed and the aqueous phase freed of dissolved ether by heating on the steam-bath for a few minutes. The optical rotation of this solution was then observed in the usual manner. The atabrine dihydrochloride concentrate was determined by spectrophotometry at the 4250 Å. band head after appropriate dilution with *p*H 2 glycine–hydrochloric acid buffer. Under these conditions the specific absorption of pure atabrine dihydrochloride was $E^{1\text{ cm.}}_{1\%}$ 198, and satisfactory agreement with Beer's law was found. The specimen of *dl*-atabrine dihydrochloride used for establishing the above extinction coefficient was found by solubility analysis to be better than 99% pure. Fraction 1 was thus found to correspond to atabrine dihydrochloride of $[\alpha]^{23}\text{D}$ +163° (dilute hydrochloric acid).

The 9 g. of fraction 1 was dissolved in 20 cc. of absolute ethanol, 60 cc. of acetone was added, and after seeding and standing overnight 6 g. (fraction 2) of acetone-washed material was obtained by filtration. Fraction 2 was found to correspond to a dihydrochloride of $[\alpha]^{23}\text{D}$ +262° (dilute hydrochloric acid).

Fraction 2 was treated like fraction 1, using the ethanol–acetone procedure, whence 3 g. was obtained of fraction 3, corresponding to dihydrochloride $[\alpha]^{23}\text{D}$ +310°. Investigation showed that it was no longer profitable to recrystallize the enriched bromocamphorsulfonate salts further, and so they were converted to the free bases by extraction of the ammoniacal solutions with ether. The ammonium 3-bromo-(*d*-camphor)-sulfonate-7 may be easily recovered from these ammoniacal mother liquors. The ether extracts of atabrine bases were treated with aqueous hydrochloric acid and on concentration of these aqueous solutions the dihydrochlorides crystallized out. In this manner fraction 3 yielded a crystalline dihydrochloride which, after drying (two hours *in vacuo* at 76°) and loss of 5.5% moisture, was found to have the following properties.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl$: C, 58.41; H, 6.82; N, 8.90. Found: C, 58.13; H, 6.73; N, 9.08. Specific rotation $[\alpha]^{23}\text{D}$ +311° (5.2 g. per 100 cc. water).

Subsequent investigation revealed that the recrystallization of either *d*-enriched or *l*-enriched atabrine dihydrochloride from water always resulted in deposition of the optically inactive racemate thus concentrating the *d* or *l* isomer in the mother liquor. The use of hot absolute ethanol as the crystallization medium circumvented this. Recrystallization of the +311° fraction from absolute ethanol yielded a product having a specific rotation of $[\alpha]^{23}\text{D}$ +355° (2.0 g. per 100 cc. water) and a specific absorption coefficient $E^{1\text{ cm.}}_{1\%}$ of 198 at 4250 Å. in *p*H 2.05 buffer. Chelintsev and Osetrova reported a value of +357° for the specific rotation of their pure dextro isomer. The material of $[\alpha]^{23}\text{D}$ +355° was used by Seeler and Malanga in their avian malaria experiments.

The mother liquors from fraction 1 deposited, on longer standing in the ice-box (2°) and after seeding with a small sample of enriched *l*-atabrine 3-bromo-(*d*-camphor)-sulfonate-7 (these seeds were obtained during a preliminary small scale pilot experiment), 6 g. (fraction 4) of a salt corresponding to dihydrochloride of specific rotation −158°. The levo enriched fraction 4 was converted to the dihydrochloride as described above, and 1.2 g. of the pure levo isomer isolated directly by recrystallization from absolute ethanol. This product was found to have a specific rotation $[\alpha]^{23}\text{D}$ of −334° (2 g. per 100 cc. water) and a specific absorption coefficient $E^{1\text{ cm.}}_{1\%}$ of 192. These values were determined on undried material. Drying for two hours at 76° *in vcauo* resulted in a weight loss of 9%.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl$: C, 58.41; H, 6.82. Found: C, 58.46; H, 7.09.

This material was also used by Seeler and Malanga in their avian malaria experiments.

Neither of the optical isomers was found by Seeler and Malanga to be more effective than the *d,l* mixture for

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(1) Present address: Philadelphia College of Pharmacy and Science.

(2) Present address: Wyeth, Inc., Philadelphia, Pa.

(3) A. O. Seeler and C. Malanga, *Proc. Soc. Exptl. Biol.*, forthcoming publication.

(4) Chelintsev and Osetrova, *J. Gen. Chem.*, *U. S. S. R.*, **10**, 1978 (1940); *C. A.*, **35**, 4029 (1941).

(5) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **67**, 356 (1895).

avian malaria, nor was any detectable difference in toxicity for mice observed.

RESEARCH LABORATORIES
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RAHWAY, NEW JERSEY
RECEIVED DECEMBER 31, 1946

Preparation of 3-Cyano-4-piperidone

BY G. BRYANT BACHMAN AND R. S. BARKER

Although N-substituted 4-piperidones have been prepared in satisfactory yields by cyclization procedures from N-alkyl-di-(β-carbethoxyethyl)-amines[1] and from N-alkyl-di-(β-cyanoethyl)-amines,[2] results with the N-unsubstituted analogs have been less gratifying.[3] We have found that di-(β-cyanoethyl)-amine may be converted to 3-cyano-4-piperidone in 70% yield by cyclizing in the presence of sodium, sodium amide or sodium alcoholates, followed by hydrolysis of the intermediate 3-cyano-4-iminopiperidine. When sodium is used as the catalyst it is desirable to use a solvent of the ether class (*e. g.*, dioxane) and to employ a metal carrier (*e. g.*, naphthalene).

Acknowledgment.—The authors are indebted to Eli Lilly and Company for financial support.

Experimental

3-Cyano-4-iminopiperidine.—Dioxane, 400 ml., distilled from sodium, was charged into a 3-neck flask equipped with a nitrogen inlet, a reflux condenser and drying tube, and an efficient stirrer. Naphthalene, 25 g., sodium, 2 g., and bis-(β-cyanoethyl)-amine,[4] 50 g., were added and the air was displaced by nitrogen. The mixture was stirred several hours on a steam-bath. The pale yellow solution gradually became cloudy and precipitated an amorphous brown solid. The product was worked up in two different ways.

Method A.—The hot reaction mixture was poured into one liter of benzene, cooled and filtered. The uncyclized amine is soluble in benzene, whereas the imine is not. The product was crystallized from ethanol, m. p. 187–188° (dec.). It can also be crystallized readily from acetone or from a mixture of dioxane and alcohol (9:1).

Method B.—The hot dioxane mixture was diluted with about 10% by volume of hot alcohol and the product allowed to crystallize. For the hydrolysis to the piperidone either the benzene or dioxane–alcohol precipitate can be used satisfactorily.

Anal. Calcd. for $C_6H_5N_3$: C, 58.48; H, 7.35; N, 34.10. Found: C, 58.46, 58.55; H, 7.21, 7.30; N, 34.05, 34.12.

Phenyl isothiocyanate derivative had a m. p. 170–171° (dec.).

Anal. Calcd. for $C_{13}H_{14}N_4S$: S, 12.37. Found: S, 12.26, 12.32.

3-Cyano-4-piperidone.—3-Cyano-4-iminopiperidine, 50 g., and 150 ml. of 5 *N* hydrochloric acid were heated to 100° for twenty minutes. The solution was cooled and neutralized to *p*H 4–5 with concentrated sodium hydroxide solution, keeping the temperature below 30°. The fine white crystals were filtered, more sodium hydroxide was added to *p*H 6–7, and the product was again filtered. This process was repeated until the filtrate became alkaline to litmus paper. The crystalline product, after washing with water and alcohol, weighed 41 g. (82% yield). To recrystallize the product it was dissolved in aqueous ammonia and vacuum distilled (water pump) on a steam-bath. The first crop of crystals appeared after half the solution had been distilled. It was filtered off and the filtrate was further concentrated to obtain a second and a third crop. The product was washed with water and alcohol. It gave a red-brown color with ferric chloride but showed no definite m. p. It was amphoteric and the titration curve showed a break at *p*H 3.1.

Anal. Calcd. for $C_6H_4ON_2$: C, 58.05; H, 6.49; total N, 22.57; amino N, 11.29. Found: C, 57.82, 57.93; H, 6.50, 6.53; total N, 22.53, 22.47; amino N (by potentiometric titration), 11.1, 11.2.

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RECEIVED FEBRUARY 5, 1947

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[1] McElvain and Stork, THIS JOURNAL, **68**, 1049 (1946).

[2] Cook and Reed, *J. Chem. Soc.*, 399 (1945).

[3] Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).

[4] Wiedeman and Montgomery, *ibid.*, **67**, 1995 (1945).

Cyanoacetal—A Correction

BY WALTER H. HARTUNG AND HOMER ADKINS

We reported in 1927 that we had obtained cyanoacetal[1] through the reaction of bromoacetal with potassium cyanide in an alcohol–water solution containing potassium iodide. Jacob van de Kamp and others have called our attention to the fact that they had been unable to obtain cyanoacetal by following the procedure described by us. Uhle and Jacobs[2] obtained cyanoacetal in 14% yield by carrying out the reaction in a manner similar to that described in our paper. They worked on a larger scale and followed a different procedure in isolating the desired product. Uhle and Jacobs graciously ignored our paper although it is clear from a comparison of the data in the two papers, that we had not isolated cyanoacetal. Since we did not have cyanoacetal in hand, the figure for the equilibrium constant reported in our paper for the reaction

$$CNCH_2CH(OC_2H_5)_2 + H_2O \rightleftarrows CNCH_2CHO + 2C_2H_5OH$$

is not significant. We regret very much our mistake and appreciate the forbearance of our friends.

Robert L. Clarke and S. M. McElvain, of this Laboratory, have obtained the same results as those reported by Uhle and Jacobs. They will publish their results in the near future as well as a description of their preferred procedure whereby cyanoacetal was prepared in excellent yield by a series of reactions through $(C_2H_5O)_2CHCH_2CO_2C_2H_5$.

[1] Hartung and Adkins, THIS JOURNAL, **49**, 2520 (1927).

[2] Uhle and Jacobs, *J. Org. Chem.*, **10**, 81 (1945).

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RECEIVED FEBRUARY 17, 1947

Equilibrium Studies on the Dehydrogenation of Primary and Secondary Alcohols. II. Cyclohexanols

BY ADRIAN H. CUBBERLEY AND MAX B. MUELLER

Free energies, heats and entropies of dehydrogenation of a number of alcohols were recently reported from this Laboratory.[1]

Further results obtained using the same appara-

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[1] Cubberley and Mueller, THIS JOURNAL, **68**, 1149 (1946).

tus and technique on cyclohexanol, 2-methylcyclohexanol and 3-methylcyclohexanol are being reported at this time.

The following heat capacity equation[1] was used for the three reactions.

$$\Delta C_p = 7.28 - 0.0118T$$

Values of ΔH_0 and I in the free energy equation

$$\Delta F = \Delta H_0 - 16.77T \log T + 0.0059T^2 + IT$$

calculated from the experimental results by the method of least squares are listed in Table I.

TABLE I

VALUES OF ΔH_0, I, ΔF_{298}, ΔH_{298}, ΔS_{298}

Alcohol	ΔH_0	I	ΔF_{298}	ΔH_{298}	ΔS_{298}
Cyclohexanol	13,588[a]	17.09	6840	15,233	28.16 ± 0.25
2-Methylcyclohexanol	13,465	17.05	6705	15,110	28.20 ± .15
3-Methylcyclohexanol	13,380	17.29	6691	15,025	27.97 ± .20

[a] ΔH_0 for cyclohexanol was calculated from Kistiakowsky's value for ΔH_{355} (Kistiakowsky, *et al.*, THIS JOURNAL, **61**, 1868 (1939)).

It is apparent that the substitution of a single methyl group ortho or meta to the hydroxyl has no appreciable effect on the thermochemistry of the dehydrogenation of cyclohexanols.

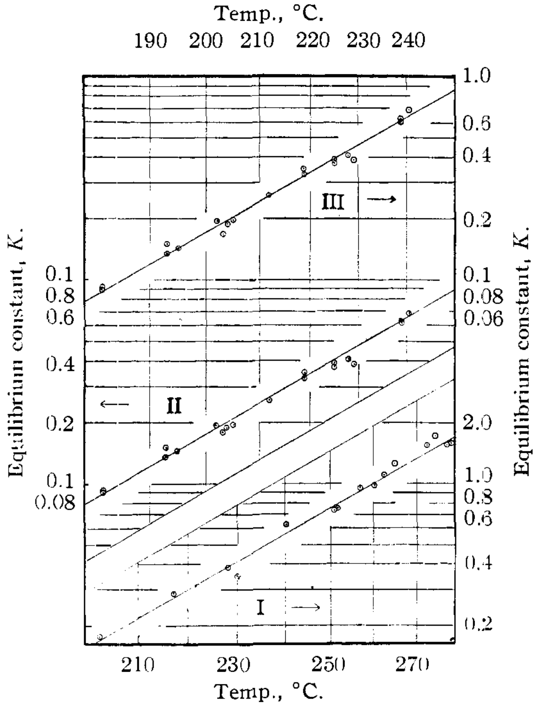

Fig. 1.—Log K *vs.* $1/T$ for dehydrogenation of: (I) cyclohexanol, (II) 2-methylcyclohexanol and (III) 3-methylcyclohexanol.

Experimentally determined values of the equilibrium constants are compared in Fig. 1, with the values calculated from the free energy equations.

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EDGEWATER, N. J.

RECEIVED JANUARY 10, 1947

Numbers of Isomeric Alkylbenzenes

BY ALFRED W. FRANCIS

The exact numbers of structurally isomeric hydrocarbons of the paraffin series,[1,2] olefin series,[3] acetylene series,[4] and of their derivatives, alcohols, etc.[2,5] (or alkyl groups), and more complex derivatives[6] are listed in the literature up to 20 to 40 carbon atoms. Each series shows a progressive increase of about 2.5 fold for each additional carbon atom so that simple equations permit approximate extrapolation to any desired extent. It does not seem to have been noted that there are slight alternations in the ratio, which in the case of paraffin isomers is higher from odd to even number of carbon atoms than from even to odd, analogous to the increments of melting points of normal paraffin hydrocarbons as shown in Fig. 1; and that like the latter, the alternation gradually subsides with increasing carbon content, although it is still detectable at C_{40}.[7]

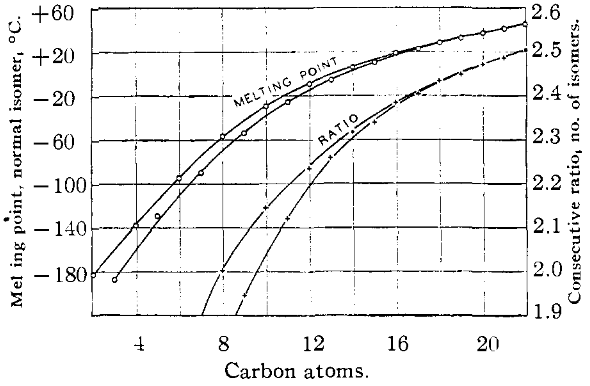

Fig. 1.—Analogy between alternations in melting points of normal paraffin hydrocarbons (physical observations) and in consecutive ratios in number of paraffin isomers (mathematical calculations).

The numbers of structurally isomeric alkylbenzenes are not listed beyond those with twelve carbon atoms[8] although mathematical equations are derived for the calculation of the number of isomers with any combination of substituents (one item in Table I).[8,9] In view of increasing

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(1) Henze and Blair, THIS JOURNAL, **53**, 3084 (1931).

(2) Perry, *ibid.*, **54**, 2919 (1932).

(3) Henze and Blair, *ibid.*, **55**, 685 (1933).

(4) Coffman, Blair and Henze, *ibid.*, **55**, 253 (1933).

(5) Henze and Blair, *ibid.*, **53**, 3045 (1931).

(6) Henze and Blair, *ibid.*, **56**, 157 (1934).

(7) Logarithmic interpolation and allowance for the alternation mentioned permitted the detection of trifling errors in the listed numbers of paraffin isomers of 29 and 40 carbon atoms. The former was recalculated by the present author, giving the number, 1,590,507,821; and the latter was recalculated by one of the original authors (H. R. Henze, private communication) giving 62,481,806,147,341. Both numbers are consistent with the logarithmic interpolation, which is accurate to about half of the figures, provided neighboring numbers are correct.

(8) Polya, *Compt. rend.*, **201**, 1169 (1935); *Helv. Chim. Acta*, **19**, 23 (1936).

(9) T. L. Hill, *J. Phys. Chem.*, **47**, 253, 413 (1943); *J. Chem. Phys.*, **11**, 294 (1943).

TABLE I

No. substituents	1	2	3	4	5	6
All alike	1	3	3	3	1	1
All different	1	3	10	30	60	60
Two alike	..	3	6	16	30	30
Three alike	..	..	3	6	10	10
Two pairs	..	..	..	11	16	16
Four alike	..	..	..	3	3	3
Two alike and three alike	..	..	..	..	6	6
Five alike	..	..	..	..	1	1
Three alike and three alike	..	..	..	..	..	3
Two alike and four alike	..	..	..	..	..	3
Three pairs	..	..	..	..	..	11

importance of aromatic hydrocarbons, the exact numbers of these isomers are now computed up to a content of 24 carbon atoms.

The numbers of isomeric derivatives of benzene are shown in Table I (this applies to any substituents, *e. g.*, Cl, NO_2).

Using this table and the numbers of isomeric alkyl groups[5] (shown also in the top line in each column of Table II) the numbers of isomeric alkylbenzenes are calculated by itemizing the types and by summation as in Table II. Thus,

TABLE II

C_{10}		C_{12}		C_{13}		C_{14}	
Bu	4	Hex	17	Hept	39	Oct	89
MePr	6	MeAm	24	MeHex	51	MeHept	117
Et$_2$	3	EtBu	12	EtAm	24	EtHex[a]	51
Me$_2$Et	6	Me$_2$Bu	24	Me$_2$Am	48	Me$_2$Hex[a]	102
Me$_4$	3	Pr$_2$	9	PrBu	24	PrAm	48
	—	MeEtPr	20	MeEtBu	40	MeEtAm	80
	22	Me$_3$Pr	12	Me$_3$Bu	24	Me$_3$Am	48
		Et$_3$	3	MePr$_2$	22	Bu$_2$	30
		Me$_2$Et$_2$	11	Et$_2$Pr	12	MePrBu	80
		Me$_4$Et[a]	3	Me$_2$EtPr[a]	32	Et$_2$Bu[a]	24
C_{11}		Me$_6$	1	Me$_4$Pr[a]	6	Me$_2$EtBu	64
			—	MeEt$_3$[a]	6	Me$_4$Bu[a]	12
Am	8		136	Me$_3$Et$_2$	6	EtPr$_2$	22
MeBu	12			Me$_5$Et	1	Me$_2$Pr$_2$[a]	38
EtPr	6				—	MeEt$_2$Pr	32
Me$_2$Pr	12				335	Me$_3$EtPr[a]	20
MeEt$_2$	6					Me$_5$Pr[a]	2
Me$_3$Et	6					Et$_4$	3
Me$_5$	1					Me$_2$Et$_3$[a]	6
	—					Me$_4$Et$_2$[a]	3
	51						—
							871

[a] Not yet represented by known hydrocarbons.

for example, there are 80 methylpropylbutylbenzenes, obtained by multiplying 4 (kinds of butyl group), 2 (kinds of propyl group), and 10 from Table I. Types containing two or more alkyl groups of like carbon content above ethyl may be subdivided according to whether these groups are alike or unlike. Thus, for tributylbenzenes, there are 3 × 4 isomers with the three substituents alike, 6 × 4 × 3 isomers with two of them alike, and 10 × 4 isomers with all three different, a total of 124.

Table II has been extended similarly for alkylbenzenes containing 15 to 24 carbon atoms. The numbers increase a little more rapidly than in the case of the paraffin isomers[1,2] so that the ratio for the two series increases steadily as shown in Table III and should exceed 1.0 at C_{28}. Again there is an alternation in ratio of successive numbers, considerable at first, but quickly subsiding as shown in Fig. 2. Extrapolation would be still more precise using the ratio to number of alkyl groups,[2,5] which approaches 0.04718 asymptotically. This would give for C_{30} 4529×10^6.

TABLE III

Carbon atoms	Numbers of isomeric: Alkylbenzenes	Numbers of isomeric: Paraffins	Ratio
7	1	9	0.1111
8	4	18	.2222
9	8	35	.2286
10	22	75	.2933
11	51	159	.3208
12	136	355	.3831
13	335	802	.4177
14	871	1,858	.4688
15	2,217	4,347	.5100
16	5,749	10,359	.5550
17	14,837	24,894	.5960
18	38,636	60,523	.6384
19	100,622	148,284	.6786
20	263,381	366,319	.7190
21	690,709	910,726	.7584
22	1,817,544	2,278,658	.7976
23	4,793,449	5,731,580	.8363
24	12,675,741	14,490,245	.8748

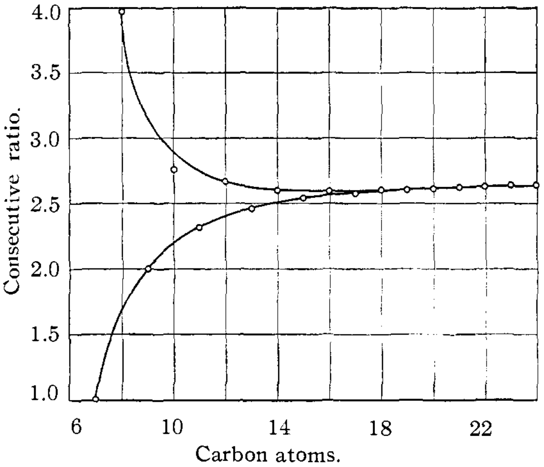

Fig. 2.—Alternations in consecutive ratios in number of isomeric alkylbenzenes.

SOCONY-VACUUM LABORATORIES
(DIVISION OF SOCONY-VACUUM OIL CO., INC.)
RESEARCH AND DEVELOPMENT DEPARTMENT
PAULSBORO, N. J.
RECEIVED FEBRUARY 24, 1947

Halogen-Metal Interconversions with Halides Containing Functional Groups

BY HENRY GILMAN AND CLYDE E. ARNTZEN[1]

In connection with studies concerned with physiological action, it was necessary to have

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TABLE I

REACTIONS OF RX COMPOUNDS WITH n-C_4H_9Li

RX	RX in		n-C_4H_9Li		Temp. of n-C_4H_9Li sol., °C.	Time of addition, min.	Stirring period, min.	Product	Yield, g.	Yield, %
	mole	ether, cc.	mole	ether, cc.						
o-BrC_6H_4OH	0.041	25	0.082	250	Room	Rapidly	40	o-HOC_6H_4COOH[a]	3.77	67
p-BrC_6H_4OH	.05	50	.1	200	Room		[b]	p-HOC_6H_4COOH		35[c]
p-IC_6H_4OH	.0437	50	.0875	190	Room	4[d]	3	p-HOC_6H_4COOH		50[e]
o-BrC_6H_4COOH	.05	100	.1	200	−75	2	10 at −75°	o-$C_6H_4(COOH)_2$	2.9	35[f]
o-IC_6H_4COOH	.05	125	.1	150	−75	4	6 at −75°	o-$C_6H_4(COOH)_2$	1	12[g]
p-IC_6H_4COOH	.05[h]		ca. .1	200	−75		4 at −75°	p-$C_6H_4(COOH)_2$		62[i,j]
p-$IC_6H_4SO_2N(C_2H_5)_2$	.02	60	ca. .02	100	−75[l]	2[k]	1	p-$HOOCC_6H_4SO_2N(C_2H_5)_2$[m]	3.7	78

[a] Identified by mixed melting point. [b] Refluxed without stirring for two hours. [c] When p-bromophenol was allowed to react with n-butyllithium for one and one-half hours, the yield of p-hydroxybenzoic acid was 41% (studies by R. W. Leeper). [d] The mode of addition was reversed in this experiment, the n-butyllithium being added to the RX compound. This is the preferred order of addition. [e] When p-iodophenol was allowed to react with n-butyllithium for twenty minutes, the yield of acid was 48% (studies by R. K. Abbott). [f] Also obtained here was 9 g. of an oil containing neutral components which was not investigated further. [g] Weight of neutral oil obtained was 11 g. [h] Powdered p-iodobenzoic acid was added in one portion to the n-butyllithium solution. [i] Weight of neutral oil obtained was 9 g. [j] In addition to the terephthalic acid formed (identified as the dimethyl ester by mixed melting point) there was recovered 7% of p-iodobenzoic acid. The separation was accomplished by extraction with acetone. Recovery of starting material indicates that an insufficient quantity of n-butyllithium was used. The experiment was carried out before the precise method for determining the titer of alkyllithium compounds was completed (see Gilman and Haubein, THIS JOURNAL, **66,** 1515 (1944)). Also the yield would probably have been improved by the reverse method of addition. [k] A bright yellow precipitate formed immediately. [l] When the interconversion was carried out at room temperature, a tar was obtained. [m] Melting point 192–194° (with turbidity). Recrystallization from ethanol or acetic acid did not raise the melting point. *Anal.* Calcd. for $C_{11}H_{15}O_4NS$: N, 5.44; neut. equiv., 257. Found: N, 5.38 and 5.41; neut. equiv., 253.

some organolithium compounds in which were contained a functional group, like hydroxyl or carboxyl. One of the better ways for the synthesis of such types is the halogen-metal interconversion reaction[1a]: $RX + R'Li \rightarrow RLi + R'X$. Some of the yields by this reaction are quite satisfactory. For example, the RLi compound from o-bromophenol is formed to an extent of at least 67%, because carbonation after interconversion gives a 67% yield of salicylic acid. By a corresponding procedure it was shown that the yields of RLi compounds from p-iodobenzoic acid and p-iodo-N,N-diethylbenzenesulfonamide were 62 and 72%, respectively.

In those cases where the functional group has an active hydrogen it is preferable to add the n-butyllithium to the RX compound so that the primary product is not consumed in a secondary halogen–metal interconversion with RX. This is illustrated by the sequence of reactions

$$o\text{-}BrC_6H_4OH + n\text{-}C_4H_9Li \longrightarrow o\text{-}BrC_6H_4OLi + n\text{-}C_4H_{10} \quad \text{(I)}$$

$$o\text{-}BrC_6H_4OLi + n\text{-}C_4H_9Li \longrightarrow o\text{-}LiC_6H_4OLi + n\text{-}C_4H_9Br \quad \text{(II)}$$

$$o\text{-}LiC_6H_4OLi + o\text{-}BrC_6H_4OH \longrightarrow C_6H_5OLi + o\text{-}BrC_6H_4OLi \quad \text{(III)}$$

Reaction (I) generally proceeds at a much more rapid rate than reaction (II). When (II) is under way, there are contained in the mixture two RLi compounds which can participate in the interconversion reaction: o-LiC_6H_4OLi and n-C_4H_9Li. The extent to which the o-LiC_6H_4OLi contributes to the interconversion results essentially in the destruction of a corresponding amount of the substituted RX compound [Reaction (III)]. Accordingly the addition of n-butyllithium to the RX compound ensures a maximum initial replacement of the active hydrogen.

Experimental

General Procedure.—The solution of the RX compound in ether was added, in the first experiments, over a short period of time to an ether solution of butyllithium. After stirring the mixture, it was carbonated by pouring over solid carbon dioxide. The product was obtained by acidification of the sodium hydroxide extract. From p-iodophenol and from o- and p-bromophenol, the hydroxybenzoic acids obtained as products were separated from the phenols by saturating the alkaline extract with carbon dioxide and extracting with ether. Details are given in the accompanying table.

p-Iodo-N,N-diethylbenzenesulfonamide.—p-Iodobenzenesulfonyl chloride was prepared from iodobenzene in accordance with the directions of Baxter and Chattaway.[2] Then, to a solution of 8 g. (0.026 mole) of the sulfonyl chloride in 100 cc. of ether was added 3.8 g. (0.052 mole) of diethylamine. After one hour, the diethylamine hydrochloride was removed by filtration and the ether solution washed with dilute hydrochloric acid followed by dilute potassium hydroxide. The yield of p-iodo-N,N-diethylbenzenesulfonamide, melting at 57–58.5° after crystallization from ethanol, was 7 g. (80%).

Anal. Calcd. for $C_{10}H_{14}O_2NIS$: N, 4.13. Found: N, 4.05.

[1a] For general references, see pp. 538–539 of Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943.

[2] Baxter and Chattaway, *J. Chem. Soc.*, **107,** 1814 (1915).

CHEMISTRY DEPARTMENT
IOWA STATE COLLEGE
AMES, IOWA

RECEIVED DECEMBER 2, 1946

4,7-Phenanthroline

BY L. HASKELBERG

4,7-Phenanthroline has been prepared from p-phenylenediamine,[1] 6-nitroquinoline,[2] and 6-ami-

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[1] Smith, THIS JOURNAL, **52,** 397 (1930); see Wibaut and coworkers, *Rec. trav. chim.*, **56,** 1219 (1937).

[2] Kuczynski and Sucharda, *C. A.*, **31,** 3921 (1937).

noquinoline.[3] It is also very easily accessible from *p*-nitroaniline.

A mixture of 338 g. of *p*-nitroaniline, 130 g. of glycerol, 84 g. of ferrous sulfate, 150 g. of nitrobenzene and 800 g. of concentrated sulfuric acid was heated until reaction set in and the reaction was then checked by discontinuing the heating. When the reaction subsided the mixture was refluxed for three hours, diluted with water, steam-distilled to remove nitrobenzene, and the solution was decolorized with 34 g. of Norit, filtered and neutralized with sodium hydroxide solution. The crude product was dried and purified by extraction with benzene in a Soxhlet apparatus or by distillation; b. p. 160° (2 mm.). Crystallization from benzene or alcohol gave needles, m. p. 173°; yield 200 g. (46%).

Anal. Calcd. for $C_{12}H_8N_2$: C, 80.0; H, 4.4. Found: C, 79.7; H, 4.5.

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[3] Kaufmann and Radosevic, *Ber.*, **42**, 2612 (1909).

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE
RECEIVED JANUARY 2, 1947

Laboratory Disposal of Mercaptan Vapors

BY HUBERT M. HILL[1] AND M. L. WOLFROM

In the course of many years of work with ethyl mercaptan (ethanethiol), the problem of its reeking odor has been ever present. We have been concerned recently with experiments employing this substance as a solvent and with its subsequent removal by evaporation techniques. We have found that these vapors readily can be adsorbed on a column of carbon impregnated with cupric chloride. This principle is not new and has been employed on a large scale by the chemical engineer.[2] Its adaptation to organic laboratory practice may, however, be of interest.

A good grade of activated carbon (6–14 mesh) of the type used for gas purification or solvent recovery, is impregnated by immersion at room temperature for twenty-four hours in a saturated aqueous solution of cupric chloride. The carbon is then removed by decantation, washed once or twice with water and dried by heating in an open dish to 130° or until hydrogen chloride fumes are evolved. One kilogram of carbon will adsorb 250–300 g. of cupric chloride. This material is then packed in a glass tube which is placed in the directed gas stream containing the volatile mercaptan. The packing converts the thiol to the disulfide with liberation of sufficient heat to require cooling by running water. The packing should be replaced before it is saturated, a condition detectable by the odor of disulfide in the exit gases.

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[1] Bristol Laboratories Research Associate of The Ohio State University Research Foundation (Project 224).

[2] *Cf.* W. L. Nelson, "Petroleum Refinery Engineering," 2nd ed., McGraw-Hill Book Co., New York, N. Y., 1941, p. 586.

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO
RECEIVED MARCH 3, 1947

Preparation of Alkyldichloramines

BY L. K. JACKSON, G. N. R. SMART AND GEORGE F WRIGHT

A method for the preparation of alkyldichloramines which is different from that of Tcherniak[1] and a modification of that of Berg[2] has been devised by close regulation of acidity or, better, by introduction of gaseous chlorine into a cold solution of sodium bicarbonate and the free amine.

The crude oils obtained by this treatment are usually sufficiently pure, on the basis of electropositive chlorine analysis by Chattaway's method,[3] that they can be used for subsequent reaction. When they are handled in this manner, especially with a slight excess of contaminant chlorine, they are fairly stable. Distilled material is relatively less stable and some of the distillations are quite dangerous.

The yield and quality of both *n*-butyldichloramine[2] and N-tetrachloro-1,2-diaminoethane[3] have been improved over those originally reported. In addition a new primary compound, *n*-octyldichloramine, has been prepared as well as three secondary dichloramines. The *n*-octyldichloramine as well as these *i*-propyl, *s*-butyl and cyclohexyl compounds were not sufficiently stable in the pure state to be shipped for elemental analysis, but were analyzed iodometrically for electropositive chlorine content.

Experimental

n-**Butyldichloramine.**—To a solution of 504 g. (6 moles) of sodium bicarbonate in 3 liters of cold water, was added 110 g. (1.5 moles) of butylamine. The mixture was maintained at 8–12° for six hours while chlorine was passed in over this period until saturation was reached. The yellow-orange oil which settled out (density *ca.* 1.1) was separated, washed with cold 5% sulfuric acid, then cold water, and dried with calcium chloride to weigh 187 g. or 88% of theoretical. When a sample was dissolved in acetic acid, treated with potassium iodide and titrated iodometrically it seemed to contain 103% butyldichloramine. The free chlorine which thus was demonstrated to be present was not removed, since it prevented decomposition to butylammonium chloride. The chlorine could be removed by washing with aqueous sodium thiosulfate. If *n*-butyl monochloramine was suspected to be present (low chlorine analyses) it could be removed by a quick wash with cold 50% sulfuric acid, followed by thorough washing with cold water.

When the molar ratio of bicarbonate to amine was decreased to 2:1 the yield was decreased to 74%; when the ratio was decreased to 3:1, the yield was increased to 92%. Although further purification was not usually necessary, the material could be distilled at 39–40° (17 mm.), (b. p. 46° (30 mm.)) d^{20}_{4} 1.108, n^{20}_{D} 1.4553. The electropositive chlorine content was 98% of theoretical.

n-**Octyldichloramine** was prepared in 76% crude yield when a 3:1 ratio of bicarbonate to amine was used. The chlorine addition time was ten hours. The crude (d^{20}_{4} 1.007) showed an electropositive chlorine content which was 97% of the calculated value.

s-**Butyldichloramine** was prepared in 96% yield using a 3:1 ratio of bicarbonate to amine over a ten-hour chlorine addition at 10°. The crude material was pure according to its electropositive chlorine content (d^{25}_{4}, 1.116).

Cyclohexyldichloramine was obtained in 95% crude yield under conditions identical with those above. A 90% recovery of product was obtained by distillation; b. p. 89–90° (17 mm.), d^{20}_{4} 1.199.

N-Tetrachloro-1,2-diaminoethane could be obtained in 92% yield only if an 8:1 bicarbonate-amine ratio was used. Chlorine addition over twelve hours at 10° yielded 70 g. of crude product from 30 g. (0.385 mole) of ethylene diamine

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[1] J. Tcherniak, *Bull. soc. chim.*, **24**, 451 (1875); *ibid.*, **25**, 160 (1876); *Ber.*, **9**, 146 (1876).

[2] A. Berg, *Ann. chim. phys.*, [7] **3**, 289 (1905).

[3] F. D. Chattaway, *J. Chem. Soc.*, **87**, 381 (1905).

hydrate. This crude material contained 96% of the theoretical electropositive chlorine content. When it was distilled at 76–78° (10 mm.) this chlorine content was found to be 99% of theoretical. The distilled product melted at 4–4.5° cor., $d^{20}{}_4$ 1.544. Since the crude material is sufficiently pure for most purposes, the distillation, which is dangerous, ought to be avoided.

i-**Propyldichloramine** was prepared by a modification of the above procedures. To an ice-cooled concentrated aqueous solution of 95 g. (1 mole) of *i*-propylamine hydrochloride (prepared *in situ*) was added slowly 2.25 moles of aqueous sodium hypochlorite (prepared by adding chlorine to cold 15% aqueous sodium hydroxide, 1.6 moles hypochlorous acid per liter). Simultaneously with this addition over two to three hours was added 6 *N* hydrochloric acid at such a rate that the acidity was maintained between *p*H 5.6 and 6.6. Brom cresol green and chlor phenol red papers can be used as criteria if the solution is allowed to creep into the paper so as to give an indicator zone ahead of the bleached zone. After two hours' subsequent stirring in the cold, the heavy oil was separated, washed once with 50 cc. cold water, twice with 50-cc. portions of 5% sodium thiosulfate, once with cold water, twice with cold 50% sulfuric acid and finally twice with cold water. The crude yield (97 g., 76% of theoretical) contained 94% of the theoretical electropositive chlorine content. Distillation at 41–43° (15 mm.) resulted in 70% recovery of yellow oil ($d^{20}{}_4$ 1.165; $n^{23}{}_D$ 1.4572) which contained 99.8% of the calculated electropositive chlorine content.

Anal. Calcd. for $C_3H_7NCl_2$: N, 10.9. Found: N, 10.6 (av.).

The authors are grateful for a grant from the National Research Council, Canada, which helped to defray the expenses of this investigation.

CHEMICAL LABORATORY
UNIVERSITY OF TORONTO
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RECEIVED FEBRUARY 21, 1947

A Modification of Wenker's Method of Preparing Ethyleneimine

BY PHILIP A. LEIGHTON, WILLIAM A. PERKINS AND MELVIN L. RENQUIST

The most convenient method for laboratory preparation of ethyleneimine is that of Wenker.[1] This is a two-step process involving the preparation of β-aminoethylsulfuric acid from monoethanolamine and sulfuric acid followed by treatment of the ester with alkali. An improved technique is suggested for the first step which involves less effort, gives a better quality of the intermediate ester, and leads to higher yields.

Six moles each of ethanolamine (b. p. 169.5–170.1°) and 95% sulfuric acid are separately diluted with half their weight of water and cooled in an ice-bath. The amine is added slowly to the acid with constant stirring in a round-bottom flask also cooled in an ice-bath. The mixture is then boiled under reduced pressure using a water aspirator attached to the flask. Bumping is prevented by the addition of glass beads and the use of a full flame to maintain vigorous boiling.

When the temperature of the liquid reaches 145°, only enough heat is applied to keep the solution boiling, and when a definite turbidity appears, usually between 155 and 160°, heating is stopped unless the temperature begins to fall. Quite suddenly crystallization takes place, causing the temperature to rise sharply to about 185°. After cooling, the cake is softened with 300 cc. of 95% ethanol, removed from the flask and ground with an additional 400 cc. of ethanol followed by filtering and drying.

The yield is 90–95%. The product is white, showing no evidence of charring as was the case when the heating was carried out in an open vessel according to Wenker's directions. Approximately one hour is required to remove the water from the above quantity of material. While Wenker was able to remove only 75% of the theoretical amount of water, in the above method a trap placed between the flask and aspirator collected virtually 100% of the amount expected.

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIFORNIA

RECEIVED MAY 5, 1947

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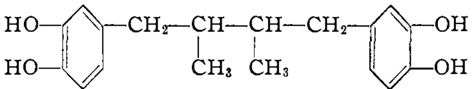
[1] H. Wenker, THIS JOURNAL, **57**, 2328 (1935).

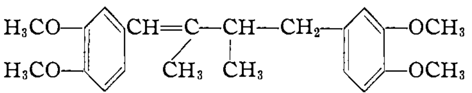
A Synthesis of Nordihydroguaiaretic Acid

BY S. V. LIEBERMAN, GEORGE P. MUELLER AND ERIC T. STILLER

Nordihydroguaiaretic acid or 2,3-*bis*-(3,4-dihydroxybenzyl)-butane [4,4¹-(2,3-dimethyltetramethylene)-dipyrocatechol] (I) is of practical interest as an antioxidant used in preserving edible fats and oils.[1] It is obtained for that purpose by the alkaline extraction of dried plants of the species *Larrea divaricata*.[2]

Schroeter and his co-workers first obtained this compound from the dimethyl ether of guaiaretic acid (II) by hydrogenation and subsequent demethylation.[3] The dimethyl ether of guaiaretic acid has since been synthesized by Haworth, *et al.*[4] These two syntheses constitute a proof of the structure of nordihydroguaiaretic acid.


I


II

The new synthesis described here confirms this structure. The first step involves the coupling of two molecules of 1-piperonyl-1-bromoethane, yielding the corresponding dimethylene ether of nordihydroguaiaretic acid (IV), a compound reported by Orcutt and Bogert as a crystalline solid, m. p. 74°.[5] Apparently a mixture of the diastereoisomers of this compound is produced by the reaction of 1-piperonylethylmagnesium bro-

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[1] U. S. Patent 2,373,192; Higgins and Black, *Oil & Soap*, **21**, 277 (1944).

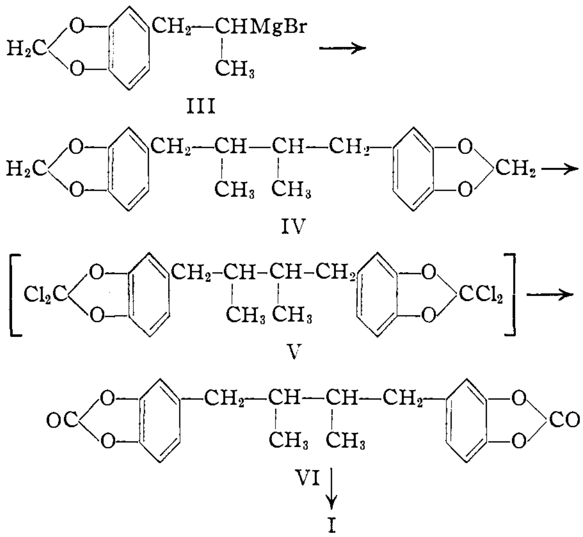
[2] U. S. Patent 2,382,475.

[3] Schroeter, Lichtenstadt and Irineu, *Ber.*, **51**, 1587 (1918).

[4] Haworth, Mavin and Sheldrick, *J. Chem. Soc.*, 1423 (1934).

[5] Orcutt and Bogert, THIS JOURNAL, **58**, 2057 (1936).

mide (III) in ethereal solution with one equivalent of iodine. While treatment with iodine gave a yield of 30%, the use of silver bromide instead of iodine gave a 21% yield. Our product was a heavy oil, b. p. 175–185° (0.1 mm.), having the correct analytical values for the dimethylene ether of nordihydroguaiaretic acid. Attempts to couple two molecules of the bromide with sodium or zinc dust in dry benzene, and with copper-bronze in decalin proved to be unsuccessful.



The dimethylene ether (IV) yielded nordihydroguaiaretic acid (I) by the following series of steps: the dimethylene ether (IV) was converted to the corresponding tetrachloro derivative (V), not isolated, which yielded the dicarbonic ester (VI) on mild hydrolysis; on saponification with acid, the dicarbonic ester (VI) yielded crystalline nordihydroguaiaretic acid (I). This product showed no depression of the melting point when mixed with an authentic sample of optically inactive nordihydroguaiaretic acid.[6]

1-(3,4-Dimethoxybenzyl)-1-bromoethane reacted with magnesium with difficulty and incompletely, yielding only 6% of the coupled product upon treatment with iodine. The phenylmagnesium bromide–cobaltous chloride free radical coupling method of Kharasch was applied.[7] None of the expected tetramethyl ether of nordihydroguaiaretic acid was obtained. The failure here, as compared to the success of this method when applied by Kharasch to the coupling of two molecules of anethole hydrobromide, may be attributed to the inactivity of the halogen in the β-position relative to its activity when adjacent to the benzene ring. The action of copper–bronze in decalin on 1-(3,4-dimethoxybenzyl)-1-bromoethane formed a small amount of heavy oil which was not further identified.

Experimental

1-Piperonyl-1-bromoethane.—Safrole, 250 g., and 200 g. of 42% hydrobromic acid were mixed in a sintered disk gas-washing bottle immersed in an ice-salt-bath. A stream of hydrogen bromide was introduced, rapidly at first, and more slowly as saturation was approached. After four hours the gas inlet was removed and the mixture permitted to stand in ice overnight. It was poured into 500 cc. of cold brine. The organic layer was diluted with ether and removed. The ether solution, washed three times with cold brine, was dried with Drierite, then anhydrous magnesium sulfate and distilled. A fraction of 218 g., b. p. 154–158° (13–14 mm.), was collected; yield 62%.

Similarly, 250 g. of methyleugenol and 121 g. of hydrobromic acid gave 326 g. of 1-(3,4-dimethoxybenzyl)-1-bromoethane, b. p. 164–167° (9.5 mm.); yield 89.5%.

2,3-bis-(3,4-Methylenedioxybenzyl)-butane (IV).—A solution of 24.3 g. (0.1 mole) of 1-piperonyl-1-bromoethane in 75 cc. of anhydrous ether was added slowly to a stirred mixture of 2.43 g. (0.1 mole) of magnesium turnings and 50 cc. of ether contained under nitrogen in the conventional Grignard apparatus. A crystal of iodine and local heating initiated the reaction which continued with refluxing by the heat of reaction for thirty minutes. After an additional hour at reflux, the heat was removed and 12.7 g. (0.05 mole) of iodine in 75 cc. of ether added to the solution. The heat of the ensuing reaction caused refluxing to resume; the small amount of unreacted magnesium dissolved quickly. After an hour of heating following this addition, the solution was cooled below 15° and hydrolyzed by the slow addition of 4% hydrochlori acid. The organic material was separated with the aid of ether and dried. A viscous, amber-colored oil, 5.0 g., was collected by distillation, b. p. 175–185° (0.1 mm.); yield 31%.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.50; H, 6.94.

2,3-bis-(3,4-Carbonyldioxybenzyl)-butane (VI).[8]—2,3-bis-(3,4-Methylenedioxybenzyl)-butane, 3.5 g., was dissolved in 15 cc. of toluene and heated at reflux for three hours with 14 g. of phosphorus pentachloride. The reaction mixture was protected from moisture. The amber-colored solution was cooled and poured slowly into 300 cc. of a stirred mixture of saturated sodium carbonate and ice and the white precipitate collected, washed with cold water and dried at 50° *in vacuo;* the yield was 1.2 g. of product, m. p. 165–168°. An additional 0.25 g. was recovered by removing and evaporating the toluene layer. After two recrystallizations from toluene the compound melted at 171.5–173°.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.80; H, 5.08. Found: C, 67.53; H, 5.41.

Nordihydroguaiaretic Acid (I).—The product from the preceding reaction, 0.68 g., was heated at reflux in an atmosphere of nitrogen with 50 cc. of 1 *N* hydrochloric acid in 80% methanol. After two and one-half hours, during which the solid slowly dissolved, the solvent was removed under reduced pressure. The residual oil was taken up in ether and extracted with 15 cc. of a 5% sodium hydroxide–3% sodium hydrosulfite solution. The aqueous layer was separated, made just acid to litmus with dilute hydrochloric acid and permitted to stand; long colorless needles, 0.16 g., separated overnight, m. p. 185.0–186.5°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.52; H, 7.28. Found: C, 71.70; H, 7.43.

A mixture of this compound with a sample of nordihydroguaiaretic acid[6] melted at 185.0–186.5°. Neither the natural nor the synthetic phenol displayed any optical rotation.

WYETH INSTITUTE OF APPLIED BIOCHEMISTRY
PHILADELPHIA, PA.
RECEIVED JANUARY 17, 1947

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[6] Purchased from Nordigard Corporation, 2536 W. Monroe Street, Chicago 12, Ill.

[7] Kharasch and Kleiman, *ibid.*, **65**, 491 (1943).

[8] *Cf. Organic Syntheses*, Coll. Vol. II, 1943, p. 549.

The Separation of *cis* and *trans* Diacetates of Cyclohexane-1,4-diol

BY THEODORE D. PERRINE[1] AND WILLIAM C. WHITE

The cyclohexane-1,4-diols have been rather extensively studied by several workers. Bayer[1a] reported the separation of the *cis* and *trans* forms through the diacetates, and gave the melting point of the *cis* form of the diacetate as 34–36°. Palfray and Rothstein have also investigated the cyclohexanediols extensively.[2] However, it was not until 1938 that Coops, Dienske and Aten[3] reported the successful separation of pure *cis*-cyclohexane-1,4-diol by employing the ditrityl ether. The pure *cis* diol melts at 112°, the diacetate at 39°. These workers showed that the diacetates formed a minimum melting eutectic composed of about 16% *trans* and 84% *cis*, melting at about 34°. They demonstrated that Bayer's *cis* diacetate of m.p. 34–36° contained 17% of *trans* isomer. Mixed melting point curves were given for the diacetates, ditrityl ethers and the free diols.

In the course of other work, we have had occasion to prepare pure *cis*-cyclohexane-1,4-diol. We have found that this may conveniently be accomplished by crystallizing a *cis–trans* mixture of the diacetates from petroleum ether, b.r. 30–60°, in conjunction with a rather simple mechanical separation. Since this separation avoids the use of the expensive trityl chloride, and also because confusion exists in the literature as to the nature of the pure *cis* diol,[4] we are reporting our results at this time.

X-Ray powder diffraction analyses of the *cis* and *trans* diacetates of cyclohexane-1,4-diol show the two forms to be distinctly different (Fig. 1).

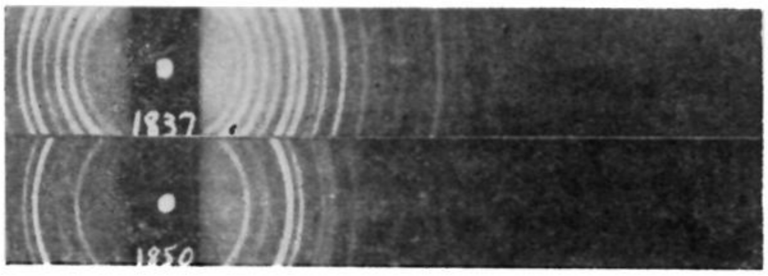

Fig. 1.—X-Ray powder diffraction patterns of *cis* (1837) and *trans* (1850) cyclohexane-1,4-diol diacetates.

The eutectic form at about 16% *trans* and 84% *cis* proved to be a simple mixture of the isomers. A prepared mixture containing 5% of the *trans* form and 95% *cis* indicated that a content of 2% or less of the *trans* isomer could be detected by X-ray powder diffraction analysis in a mixture of the two forms. The X-ray diffraction patterns were obtained using a commercial X-ray diffraction unit utilizing a copper target with a 0.00035 in. nickel filter giving essentially CuK$_\alpha$ radiation. The powdered sample was mounted on a wedge-type holder at the center of a cylindrical camera of 14.32 cm. diameter. The X-ray powder diffraction data are given in the conventional manner in

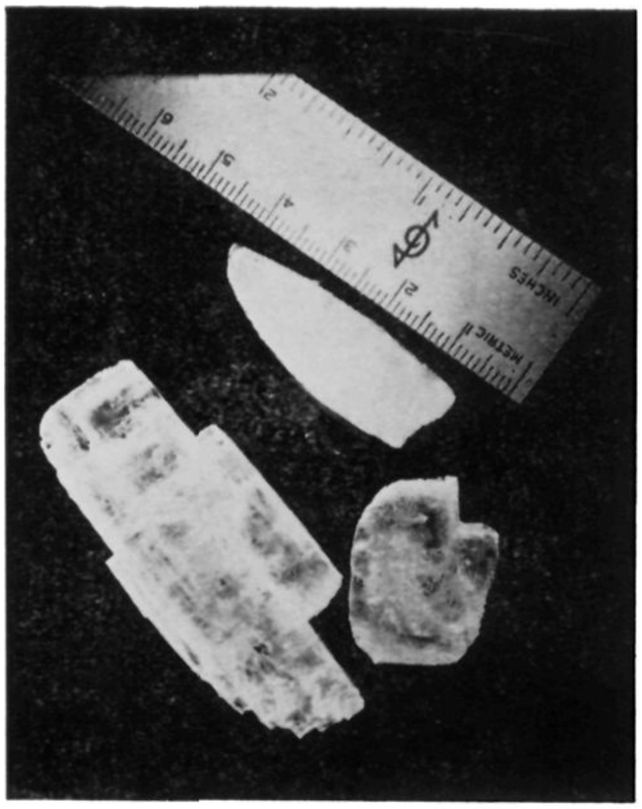

Fig. 2.—Crystals of *cis*-cyclohexane-1,4-diol diacetate.

TABLE I

Cis		*Trans*	
d^a	$I/I_0{}^b$	d	I/I_0
7.2	0.21	6.6	0.25
6.24	.76	5.62	.03
5.36	.55	5.32	.09
4.76	.22	4.40	1.00
4.24	1.00	4.04	0.37
3.90	0.60	3.51	.18
3.56	.10	3.36	.15
3.42	.28	3.30	.23
3.09	.50	3.23	.15
2.92	.01	2.93	.16
2.88	.04	2.85	.07
2.75	.15	2.79	.06
2.63	.04	2.67	.04
2.56	.06	2.37	.01
2.38	.06	2.29	.03
2.33	.06	2.13	.03
2.18	.06	2.03	.04
2.05	.18	1.94	.03
1.97	.06	1.86	.01
1.89	.04	1.80	.20
1.78	.02	1.75	.01
1.75	.06	1.70	.03
1.65	.01	1.60	.01
1.60	.01		
1.57	.01		

[a] d is the interplanar spacings in ångström units.
[b] I/I_0 gives the relative intensities of the lines as measured with a recording microphotometer.

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(1) Present address: Department of Chemistry, Montana State College, Bozeman, Montana.

(1a) Bayer, *Ann.*, **278**, 92 (1894).

(2) One of the most extensive papers in this field is that of Rothstein in *Ann. Chim.*, **14**, 461–598 (1930).

(3) Coops, Dienske and Aten, *Rec. trav. chim.*, **57**, 303–315 (1938).

(4) Olberg, Pines and Ipatieff, THIS JOURNAL, **66**, 1096–1099 (1944).

Table I. The X-ray crystallography of the *trans* diacetate has been reported by T. N. White.[5]

Experimental

Cyclohexanediol[6] (471 g.), prepared by the catalytic hydrogenation of hydroquinone, was acetylated with 8.12 equivalents of acetic anhydride by refluxing two hours. The acetylation mixture was allowed to stand at room temperature several days. The volatile material was distilled off at 10 mm. on the steam-bath. The distillate weighed 620 g. The residue crystallized on cooling. The diacetate crystals were filtered at 38°, washed twice with a small amount of alcohol and dried *in vacuo*, m. p. 102.5–103.5°.

The mother liquors were poured into water, extracted with ether, dried with anhydrous potassium carbonate, the ether removed and the residue crystallized from about 300 cc. of alcohol. The first crop weighed 280 g. This material was crystallized from petroleum ether (b. r. 30–60°) (Skellysolve "F"). Two forms of crystals were obtained. The *trans* form crystallized as fragile needles, while the *cis* form came down as massive prisms or as rosets. By vigorously shaking the dried product the *trans* crystals were broken up and the *cis* form was easily picked out. The crude *cis* form thus obtained melted at 35–37°. This was dissolved in petroleum ether, and when cold seeded with a well-formed *cis* crystal. The *cis* form crystallized at once. By carefully watching the course of the crystallization it was easy to observe the formation of the first needles of the *trans* diacetate. At this point the liquid was decanted from the *cis* crystals. One or two more crystallizations from petroleum ether sufficed to remove impurities and to yield a *cis* form with a freezing point of 41.25°. Coops, *et al.*, give 39° as the melting point of this isomer. Typical crystals are shown in Fig. 2. The refractive index of the pure *cis* form (supercooled liquid) was $n^{25}\mathrm{D}$ 1.4508 and $n^{22.2}\mathrm{D}$ 1.4518. The b. p. at 760 mm. was 251°.

Anal. Calcd. for $C_{10}H_{16}O_4$ (*cis*): mol. wt., 200.23; C, 59.98; H, 8.06. Found: C, 60.25; H, 7.98.

Hydrolysis was accomplished by boiling for four hours with four times the weight of barium hydroxide octahydrate in 25 volumes of water. Carbon dioxide was passed in to precipitate excess barium, and the solution filtered, evaporated to dryness, and extracted with acetone. The acetone was concentrated, filtered and the solution allowed to crystallize. The product melted at 112.4–112.8°.

Coops, *et al.*, give 112° as the melting point of the pure *cis* form.

---

[5] T. N. White, *Z. Krist.*, **80**, 5–17 (1931).

[6] We are indebted to Dr. Nathan L. Drake, at University of Maryland, for supplying us with a generous amount of cyclohexane-1,4-diol.

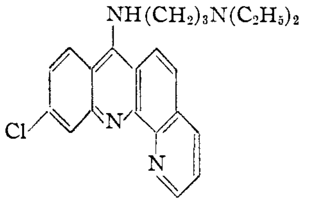
CONTRIBUTION FROM THE
DIVISION OF PHYSIOLOGY AND THE
INDUSTRIAL HYGIENE RESEARCH LABORATORY,
NATIONAL INSTITUTE OF HEALTH
BETHESDA 14, MARYLAND

RECEIVED JANUARY 9, 1947

The Preparation of 10-Chloro-7-(3-Diethylaminopropylamino)-pyrid[3,2-*c*]acridine[1]

BY H. R. SNYDER AND HERBERT E. FREIER[2]

During the recent search for new antimalarials it seemed of interest to prepare for testing 10-chloro-7-(3-diethylaminopropylamino)-pyrid[3,2-*c*]acridine (I), which is closely related chemically to atebrin (II) but which has the additional heterocyclic ring.



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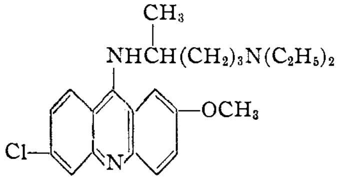

II

By the use of experimental conditions similar to those employed[3] in the condensation of *p*-anisidine with 2,5-dichlorobenzoic acid, 8-aminoquinoline was condensed with 2,4-dichlorobenzoic acid to give 8-(2-carboxy-5-chlorophenylamino)-quinoline in 55% yield. This substance readily underwent the expected cyclization and the product reacted with phosphorus oxychloride to form 7,10-dichloropyrid[3,2-*c*]acridine in 38% yield. The desired drug (I) was obtained by heating the dichloro compound with 3-diethylaminopropylamine at 100–110° for two hours; it was isolated only as the picrate. Because of the fact that it became necessary to abandon the project before the synthesis could be repeated on a preparative scale, the work is being reported in its present form.

Experimental

8-(2-Carboxy-5-chlorophenylamino)-quinoline.—A 150-ml. three-necked flask, fitted with a stirrer and a partial reflux condenser, containing 15 g. of 8-aminoquinoline, 14.3 g. of 2,4-dichlorobenzoic acid, 10.4 g. of potassium carbonate, 0.05 g. of copper bronze and 30 ml. of *n*-hexanol was placed in an oil-bath. The contents were well stirred and the temperature of the oil-bath was kept at 180°. After the solution had been heated for about twenty minutes the contents solidified; however, the mixture was heated for an additional two hours at the above temperature. The pasty brown solid was added to water and the mixture was steam distilled. The brown solution (400 ml.) remaining in the distilling flask was filtered while hot and as the solution cooled the green potassium salt precipitated. After additional water had been added, the mixture was heated to boiling to dissolve the salt. The solution was made acidic with acetic acid and the green solid was collected by filtration and washed with water. The crude product after being dried in an oven at 80° weighed 13 g. (55%).

The substance after recrystallization from xylene melted at 246–249°.

Anal. Calcd. for $C_{16}H_{11}O_2ClN_2$: C, 64.23; H, 3.71. Found: C, 64.45; H, 3.71.

10-Chloro-7-hydroxy-pyrid[3,2-c]acridine.—In a 50-ml. flask was placed a mixture of 7 g. of crude 8-(2-carboxy-5-chlorophenylamino)-quinoline and 12 ml. of

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

[2] Present address: Department of Chemistry, the University of North Dakota, Grand Forks, North Dakota.

[3] Feldman and Kopeliowitsch, *Arch. Pharm.*, **273**, 488 (1935).

concentrated sulfuric acid (sp. gr. 1.84). The mixture was heated on a steam-bath for four hours and then poured into 120 ml. of boiling water. After the mixture had been boiled for five minutes, the yellow precipitate was collected by filtration. The moist solid was boiled for five minutes with a solution of 3.5 g. of sodium carbonate in 45 ml. of water, collected by filtration and washed well with water. The crude product weighed 6 g. (92%). After recrystallization from glacial acetic acid the pure yellow compound melted at 315–320° (block).

Anal. Calcd. for $C_{16}H_9OClN_2$: C, 68.46; H, 3.23. Found: C, 68.32; H, 3.21.

7,10-Dichloro-pyrid[3,2-c]acridine.—The experimental conditions were patterned after those of Albert and Ritchie[4] for the preparation of 9-chloroacridine. In a 50-ml. three-necked flask fitted with a stirrer and reflux condenser, 25 ml. of phosphorus oxychloride was heated to 90° and 5 g. of the crude hydroxy compound was added. The temperature of the bath was then raised to 130–140° and maintained at this temperature for two hours. The excess phosphorus oxychloride was removed by distillation and the residual black tarry substance solidified on cooling. This material was added to 20 ml. of ammonium hydroxide and 50 g. of ice and the mixture was stirred vigorously and then filtered. The greenish brown solid melting at 170–200° weighed 4 g. To this material was added 100 ml. of ethyl alcohol; the mixture was heated under reflux for a few minutes and then filtered. A dilute solution of ammonium hydroxide (0.5%) was added to the brown filtrate until precipitation occurred. The mixture was cooled in an ice-bath and the solid was collected on a Büchner funnel. After three recrystallizations, the light green solid melting at 222–225° weighed 2 g. (38%).

Anal. Calcd. for $C_{16}H_8N_2Cl_2$: C, 64.23; H, 2.69. Found: C, 63.99; H, 2.76.

10-Chloro-7-(3-diethylaminopropylamino)-pyrid[3,2-c]acridine.—A mixture of 0.5 g. of the chloro compound and 2 g. of dry 3-diethylaminopropylamine (dried over solid potassium hydroxide for twelve hours and then distilled) was heated at 100–110° for two hours. To the red solution was added 3 ml. of 15% sodium hydroxide and 25 ml. of ether. After the mixture had been stirred the ether layer was separated and washed five times with 10-ml. portions of water to remove any excess 3-diethylaminopropylamine. The ether solution was dried over potassium carbonate, filtered and the solvent was removed by distillation. The residual red oil (0.3 g.) was dissolved in ethyl alcohol and to this solution was added a saturated solution of picric acid in ethyl alcohol. The dipicrate after three recrystallizations from nitromethane melted at 213–216°.

Anal. Calcd. for $C_{35}H_{31}ClN_{10}O_{14}$: C, 49.38; H, 3.67. Found: C, 49.36; H, 3.90.

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[4] Albert and Ritchie, "Organic Syntheses," **22**, 5 (1942).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

RECEIVED FEBRUARY 15, 1947

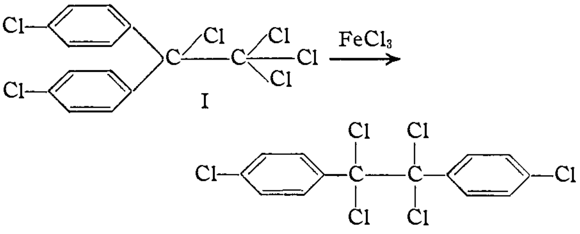
[CONTRIBUTION FROM HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Rearrangement of 1,1,1,2-Tetrachloro-2,2-bis-(*p*-chlorophenyl)-ethane, "Chloro-DDT," to 1,1,2,2-Tetrachloro-1,2-bis-(*p*-chlorophenyl)-ethane

BY W. L. WALTON[1]

It has been shown[1a] that 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane (DDT) yields an equivalent of hydrogen chloride and 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethylene when treated with ferric chloride. No rearrangement was involved in this reaction.

In our laboratories a study was made of the effect of anhydrous ferric chloride on the compound in which the tertiary aliphatic hydrogen atom of DDT had been replaced by a chlorine atom. During the course of this work with 1,1,1,2-tetrachloro-2,2-bis-(*p*-chlorophenyl)-ethane (I) the following interesting rearrangement was observed:



The product "1,1,2,2-tetrachloro-1,2-bis-(*p*-chlorophenyl)-ethane" or, systematically, *p*,*p*′-α,α,α′,α′-hexachlorobibenzyl (II) was obtained in 85% yield when molten (I) was heated for fifteen seconds with a trace of ferric chloride. The reaction was strongly exothermic. Long heating of the tetrachloroethane (I) with ferric chloride altered the course of the reaction leading to the evolution of much hydrogen chloride and a dark viscous reaction mixture from which none of (II) could be isolated.

The chief product of this rearrangement, hexachlorobibenzyl (II) is a known compound.[2] In our work its identity was established by synthesis from α,α,α,*p*-tetrachlorotoluene[2] and by its conversion to the known derivatives 4,4′-dichlorotolane,[2] and 4,4′-dichlorobenzil.[3]

Experimental

Rearrangement.—Fifteen grams of 1,1,1-trichloro-2-chloro-2,2-bis-(*p*-chlorophenyl)-ethane (I)[4] was heated to 160° and 5 mg. of anhydrous ferric chloride was stirred into the melt. The melt turned blue, evolved hydrogen chloride, and its temperature rose rapidly to 210°. The mixture was immediately cooled to room temperature by rapidly transferring the reaction vessel to an ice–water-bath. Solidification began before the temperature indicated by the thermometer reached 170°. The crystalline mass was pulverized under 20 ml. of carbon tetrachloride while being heated on a steam-bath, and then cooled and filtered. The yield of gray-white crude product was 12.75 g. (85% of theoretical); it melted at 189–192°. One recrystallization from carbon tetrachloride raised the melting point to 193–194°. Kenner and Witham[2] reported m. p. 190° (apparently uncorrected).

Anal. Calcd. for $C_{14}H_8Cl_6$: Cl, 54.70. Found: Cl, 55.0.

***p*,*p*′-Dichlorobenzil.**—A mixture of 1 g. of the hexachlorobibenzyl (II), 40 ml. of glacial acetic acid and 10 ml. of water was placed in a sealed Pyrex tube and heated in an oil-bath at 160–175° for thirty-six hours. After cooling to room temperature, the tube was opened and the solid

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[1] Present address: General Electric Company, Schenectady, N. Y.

[1a] Fleck and Haller, THIS JOURNAL, **66**, 2095 (1944).

[2] Kenner and Witham, *J. Chem. Soc.*, **97**, 1960 (1910).

[3] Liebeman and Homeyer, *Ber.*, **12**, 1971 (1879).

[4] Grummitt, Buck and Jenkins, THIS JOURNAL, **67**, 155 (1945).

product, 0.71 g. of yellow needle-like crystals, m. p. 193–194°, was collected on a filter. The product was purified by several successive crystallizations from carbon tetrachloride and ethanol to a constant melting point, 198–199°. Melting points reported previously are 200°[5] and 193°.[2]

***p,p'*-Dichlorotolane.**—A mixture of 2.0 g. of hexachlorobibenzyl (II) and 2.0 g. of zinc dust was refluxed for forty-eight hours in 200 ml. of anhydrous ethanol. The mixture was filtered hot to remove unused zinc and the filtrate cooled to room temperature. The platelets, 0.5 g., which precipitated, melted at 178–179°. The melting point previously reported[2] is 175–176°.

Synthesis of *p,p,'*,α,α,α',α'-Hexachlorobibenzyl from α,α,α,*p*-Tetrachlorotoluene.—This reaction was carried out according to the directions of Kenner and Witham[2] using 12 g. of α,α,α,*p*-tetrachlorotoluene (b. p. 152–155° (70 mm.)) and 8.3 g. of copper powder which was reduced[6] by alcohol vapor in a heated tube. The product, 3.2 g., melted at 193–194° and gave no depression in melting point when mixed with the hexachlorobibenzyl from the rearrangement.

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(5) Montagne, *Rec. trav. chim.*, [ii] **21**, 19 (1902).

(6) Eiloart, THIS JOURNAL, **12**, 239 (1890).

GENERAL ELECTRIC COMPANY
SCHENECTADY, N. Y.
RECEIVED JANUARY 20, 1947

Dehydrogenation of 1,5-Pentanediol

BY L. E. SCHNIEPP AND H. H. GELLER[1]

Recently reported preparation of γ-butyrolactone[2] and γ-valerolactone[3] by catalytic dehydrogenation of 1,4-butanediol and 1,4-pentanediol, respectively, suggested that δ-valerolactone might be prepared in a similar manner from the now readily available 1,5-pentanediol.[4]

Dehydrogenation was found to proceed smoothly on heating 1,5-pentanediol with a copper chromite[5] catalyst, δ-valerolactone being obtained in 78% crude yield. It was found advantageous to stop the reaction after about 85% of the theoretical amount of hydrogen had been evolved. Attempts to carry the dehydrogenation to completion resulted in the formation of 30–35% of polymeric products.

Vacuum distillation of the dehydrogenation reaction mixture yielded a product which analyzed about 90% δ-valerolactone and 10% 1,5-pentanediol. Refractionation improved the purity up to 97–98%. Complete removal of contaminating diol was effected by adding a slight excess of phenyl isocyanate to the mixture, decomposing the excess with water and distilling the pure lactone from the residue of the bis-phenylurethan and diphenylurea. A 71% yield of pure δ-valerolactone was obtained by this procedure. This compares favorably with the method involving the hydrolysis of δ-chlorovaleronitrile.[6]

Dehydrogenation of 1,5-Pentanediol.—1,5-Pentanediol, 52 g. (0.50 mole), was thoroughly mixed with 1.5 g. of copper chromite and the mixture was heated under reflux. The top of the reflux condenser was connected to a gas-washing bottle, containing water, which was in turn connected to a wet-test meter. Vigorous evolution of hydrogen began when the temperature of the reaction mixture reached 210° and continued for about thirty minutes. At the end of this time the temperature had risen to 245° and gas evolution slowed down considerably. Meter readings showed that 21 liters of gas had been evolved. Heating was stopped and the reaction mixture subjected to vacuum distillation. The distillate, 43.2 g., was analyzed by saponification with 0.4 *N* sodium hydroxide and found to consist of 90.6% δ-valerolactone. Treatment of another sample with phenyl isocyanate yielded a precipitate of the bis-phenylurethan of 1,5-pentanediol. The weight of urethan obtained was roughly equivalent to 9.4% of diol in the original sample. Refractionation of this crude product gave a distillate analyzing 97–98% pure as the lactone. The yield of crude lactone based on the analysis of the original distillate was 78.3% of the theoretical.

Purification of δ-Valerolactone.—A sample of the crude distillate from the dehydrogenation was treated with a 10% excess of phenyl isocyanate over that calculated as necessary to react with the 1,5-pentanediol in the sample. This mixture was shaken and allowed to stand for thirty minutes after which sufficient water to react with the excess phenyl isocyanate was added. The resulting mixture was distilled under reduced pressure. The distillate analyzed as 100% δ-valerolactone by saponification and the yield calculated back to the original 1,5-pentanediol was 71.2% of the theoretical. The pure lactone had the following properties: b. p. 105° (8 mm.) (227° (750 mm.)), n^{25}_{D} 1.4553, d^{25}_{4} 1.104.

The structure of the lactone was established by converting a sample to δ-iodovaleric acid, m. p. 56–57°. Mixed melting point with an authentic sample showed no depression.

NORTHERN REGIONAL RESEARCH LABORATORY[7]
UNITED STATES DEPARTMENT OF AGRICULTURE
PEORIA 5, ILLINOIS
RECEIVED FEBRUARY 24, 1947

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(1) Formerly Chemist, Industrial Chemical Section, Agricultural Residues Division.

(2) (a) J. W. Reppe, *Chem. Industries*, **57**, 458 (1945). Condensation of translated report on advances in acetylene chemistry by Dr. J. W. Reppe, ORR Report No. G-1, Rubber Reserve Co. (July 25, 1945); (b) I. G. Callomon and G. M. Kline, *Modern Plastics*, **23**, No. 6, 174 (1946); (c) Krizikalla, OPB Report No. 11431, U. S. Department of Commerce (February 19, 1943).

(3) L. P. Kyrides and F. B. Zienty, THIS JOURNAL, **68**, 1385 (1946).

(4) L. E. Schiepp and H. H. Geller, *ibid.*, **68**, 1646 (1946).

(5) "Organic Syntheses," Coll. Vol. II, p. 142.

(6) H. Kroper and Bretschneider, OPB Report No. 645, U. S. Department of Commerce (April 25, 1942).

(7) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

Estrogenic Action and Isomorphism

BY HERBERT E. UNGNADE AND FRANCIS V. MORRISS

The extraordinary agreement in the molecular dimensions of stilbestrol and estrone[1] and the dihydrostilbestrol isomers and estrone[2] as determined from crystallographic data has prompted a study of the melting behavior of mixtures of natural and synthetic estrogens.

The results prove that mixed crystals are formed between α-estradiol and the synthetic estrogens stilbestrol (Fig. 1) and *meso*-dihydrostilbestrol (Fig. 2) and hence the isomorphism of these substances, but it is uncertain whether the solid solutions are continuous or not at the melting temperatures. The same uncertainty holds for the system of mixed crystals between stilbestrol and *dl*-dihydrostilbestrol (Fig. 3), whereas the dia-

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(1) Giacomello and Bianchi, *Gazz. chim. ital.*, **71**, 667 (1944).

(2) Carlisle and Crowfoot, *J. Chem. Soc.*, 5 (1941).

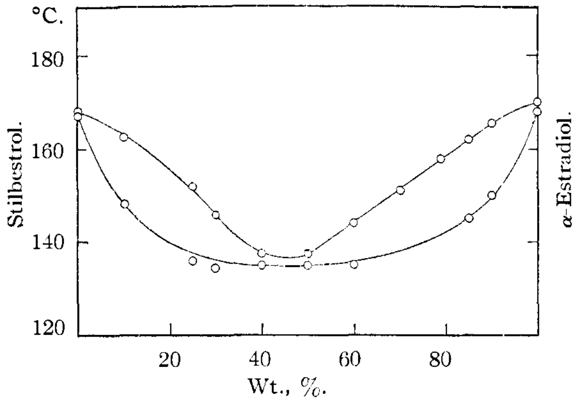

Fig. 1.

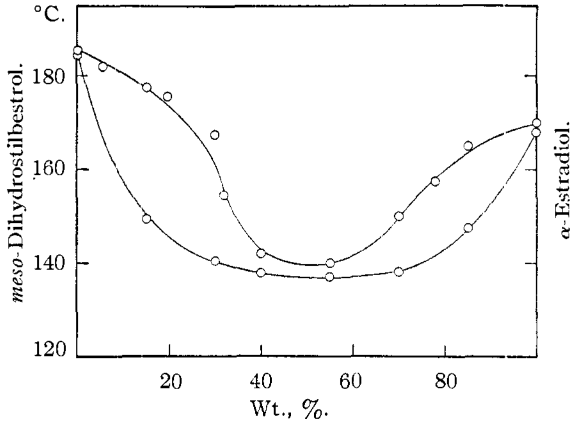

Fig. 2.

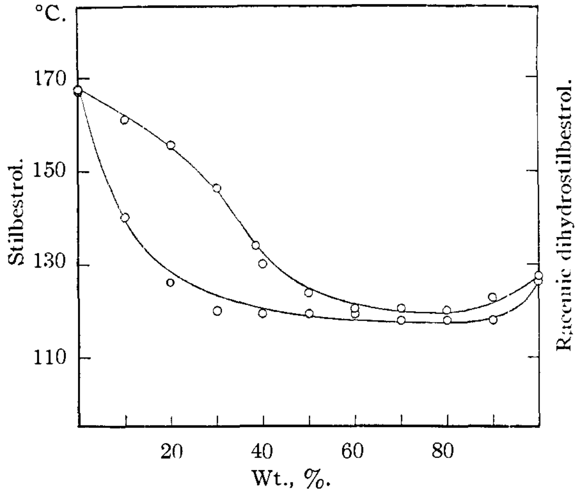

Fig. 3.

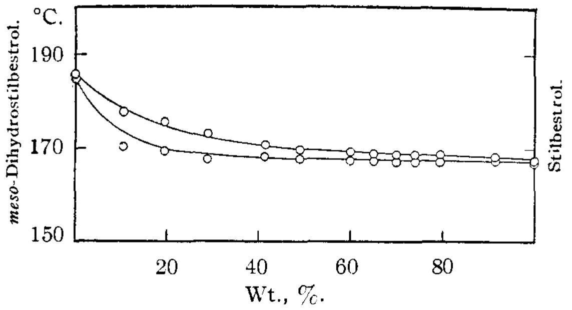

Fig. 4.

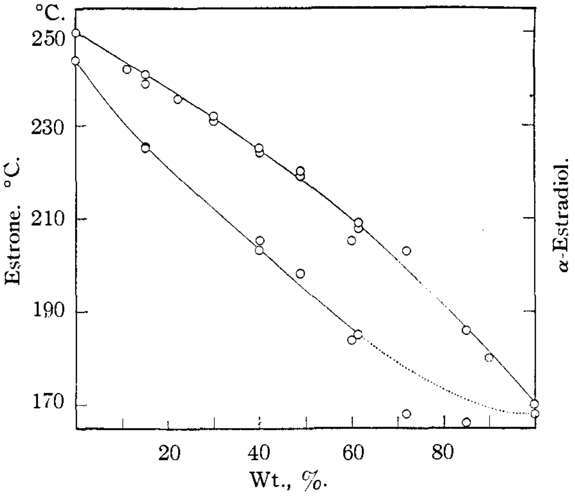

Fig. 5.

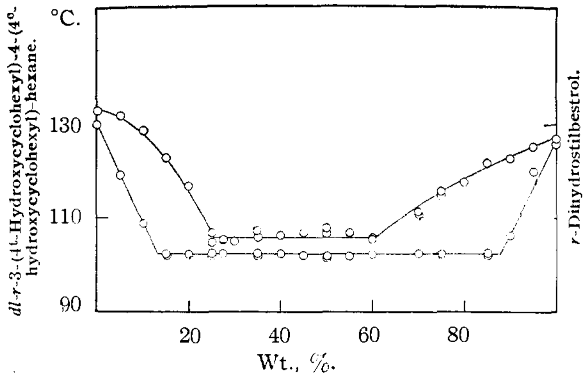

Fig. 6.

gram for the system stilbestrol-*meso*-dihydrostilbestrol (Fig. 4) is fairly conclusive as an indication of complete miscibility of the solids.

The observed formation of mixed crystals between stilbestrol and its dihydro compounds further substantiates the *trans*-configuration of the stilbestrol isomer melting at 171°[3] since *cis*-stilbenes do not form solid solutions with the corresponding dihydro compounds.[4]

The natural estrogens estrone and α-estradiol give an indication of mixed crystal formation (Fig. 5). The experimental difficulties in this case are however so great that the data are subject to considerable uncertainty.

All of the compounds described above form mixed crystals and are biologically active as estrogens. The perhydrostilbestrol compounds[5] which presumably have similar dimensions[6] are biologi-

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[3] Solmssen, *Chem. Rev.*, **37**, 504 (1945).

[4] Neuhaus, *Die Chemie*, **57**, 34 (1944).

[5] Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945).

[6] Schueler, *Science*, **103**, 221 (1946).

cally inactive.[7] An investigation of one of these, *dl-r*-3(4^t^-hydroxycyclohexyl)-4-(4^c^-hydroxycyclohexyl)-hexane, has failed to show any appreciable mixed crystal formation with the corresponding active dihydro compound (Fig. 6).

Experimental[8]

The melting point diagrams (Figs. 1–6) were obtained in an ordinary melting point apparatus according to the procedure of Rheinboldt[9] or Grimm.[10] The lower curves in the diagrams (solidus curves) represent the thawing points (first appearance of liquid), the upper curves (liquidus curves) the final melting temperatures (clear melt). All mixtures were stirred continuously after thawing in order to insure equilibrium conditions. Fusing of the samples (method of Rheinboldt) was applicable only for mixtures of stilbestrol and *dl*-dihydrostilbestrol (Fig. 3). Mixtures containing α-estradiol resolidified only partially after melting. The determinations were therefore carried out with carefully ground mixtures (method of Grimm) which were heated to 125° for twelve hours prior to the determination.

Mixtures of *dl*-dihydrostilbestrol and *dl-r*-3-(4^t-hydroxycyclohexyl)-4-(4^c-hydroxycyclohexyl)-hexane did not solidify after melting, and a diagram obtained from freshly prepared mechanical mixtures showed considerable lack of equilibrium. The values in Fig. 6 were obtained from finely ground mechanical mixtures which were kept at room temperature for several months or which were maintained at 80° for twelve hours. The curves show two eutectic points and the formation of a compound. The maximum in this case is flattened out so that the eutectic points are connected by a nearly straight line. A diagram of this type has been described by Rheinboldt[9a] for the system *m*-hydroxybenzaldehyde–picric acid. As in the example of Rheinboldt, the thaw curve in Fig. 6 does not coincide with the melting curve in the flat part between the two eutectic points. This is believed to be due to the fact that the perhydro compound was not entirely pure. A higher melting point (135°) has been reported for this compound.[11]

The data in Fig. 5 were obtained by preheating the mixtures to 165° for at least twenty-four hours in an atmosphere of oxygen-free nitrogen. The uncertainties in this case are due to the fact that the samples darken during the determinations presumably due to oxidation. Mechanical mixtures which were not preheated gave thaw points which could not be reproduced for all percentages. Sufficient points were obtained to deduce at least limited miscibility.

Acknowledgment.—The authors are indebted to Dr. W. M. Hoehn, George Breon Co., Kansas City, Mo., for a supply of the hormones used in this investigation.

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[7] Unpublished work by J. Leon Sealy, George Breon Co., Kansas City, Missouri.

[8] All temperatures uncorrected.

[9] (a) Rheinboldt, *J. prakt. Chem.*, [2] **111**, 242 (1925); (b) Rheinboldt, *ibid.*, **112**, 187 (1926); **113**, 199, 348 (1926).

[10] Grimm, Günther and Tittus, *Z. physik. Chem.*, **B14**, 180 (1931).

[11] Schoeller, Inhoffen, Steinruck, and Höss, U. S. Patent 2,392,846 (1946).

CHEMISTRY DEPARTMENT
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RECEIVED SEPTEMBER 9, 1946

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o-Acetobenzoic Acid, its Preparation and Lactonization. A Novel Application of the Doebner[1] Synthesis

BY HARRY L. YALE

We have found that phthalic anhydride and malonic acid, in the presence of pyridine, give acetobenzoic acid in 48.5% yield; the only other product, aside from unreacted phthalic anhydride, is *o*-phthalic acid. The reaction probably proceeds through the intermediate formation of phthalylacetic acid since small amounts of that compound are obtained from the same reactants under special conditions. 3-Methylenephthalide is another intermediate whose transitory existence during this reaction is possible. Both of these compounds have been reported to yield *o*-acetobenzoic acid.[1a,2]

We have also found that *o*-acetobenzoic acid lactonizes to 3-methylenephthalide when heated with acetyl chloride.

***o*-Acetobenzoic Acid.**—A finely ground mixture of 52.7 g. (0.36 mole) of phthalic anhydride and 44.0 g. (0.42 mole) of malonic acid (dried in an oven at 100° for two hours) was heated on a steam-bath for three hours with 35 ml. of Mallinckrodt reagent grade pyridine. Carbon dioxide was evolved during the entire heating period. The clear yellow solution was diluted with 300 ml. of water which caused a colorless solid, m. p. 124–126°, to separate. This was filtered and dried. The 10 g. of material thus obtained was identified as unreacted phthalic anhydride by a mixed melting point. When the filtrate was treated with 17 ml. of concentrated hydrochloric acid (*p*H of solution resulting was 3.9) and allowed to stand for three days at room temperature, clusters of needles formed on the sides of the flask. These were filtered off; weight 15.3 g. After one recrystallization from 100 ml. of benzene there was obtained 14.5 g. of colorless needles, m. p. 114–115°. *o*-Acetobenzoic acid is reported to melt at 115°.[3]

The filtrate from the acetobenzoic acid was treated with 18 ml. of concentrated hydrochloric acid. The solid which separated weighed 21.6 g. This was heated under reflux with 250 ml. of benzene and filtered hot. The benzene filtrate on cooling yielded an additional 10.5 g. of acetobenzoic acid, m. p. 114–115°. The benzene insoluble material, 11.1 g., was recrystallized from 110 ml. of boiling water, m. p. 200–201° (dec.). *o*-Phthalic acid is reported to have a m. p. of 206–208° (dec.).

Anal.[4] Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.62. Found: C, 57.75; H, 3.95. An additional 3.0 g. of crude acetobenzoic acid was obtained by the ether extraction of the filtrate from which the mixture of two acids had been obtained. The total yield of acetobenzoic acid was 48.5%.

o-Acetobenzoic acid forms a normal 2,4-dinitrophenylhydrazone, m. p. 185–186°.

Anal. Calcd. for $C_{15}H_{12}O_6N_4$: N, 16.28. Found: N, 15.93.

Isolation of Phthalylacetic Acid.—A mixture of 52.0 g. (0.5 mole) of malonic acid, 74.0 g. (0.5 mole) of phthalic anhydride and 50 ml. of pyridine was allowed to stand at room temperature for eleven days and was then diluted with 350 ml. of water. The solid which separated weighed 54.8 g. and was identified as phthalic anhydride. The filtrate was made acid to congo red and cooled. The solid obtained was collected, extracted with boiling benzene and filtered hot. On cooling there was obtained an additional 8.0 g. of phthalic anhydride. The benzene insoluble material was dissolved in 200 ml. of dioxane. On cooling, two types of crystals separated: (1) opaque plates and (2) large transparent clusters. These were separated mechanically. The plates, m. p. 270° (dec.), 2.0 g., were phthalylacetic acid.

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.16; H, 3.16; neut.

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[1] Roger Adams, editor, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, volume 1, pp. 226, 233.

[1a] Gabriel and Michael, *Ber.*, **10**, 1551 (1877).

[2] Gabriel, *ibid.*, **17**, 2521 (1884).

[3] Benneville, *J. Org. Chem.*, **6**, 462 (1941).

[4] The microanalyses were carried out by Mr. J. F. Alicino of this Institute.

equiv., 190. Found: C, 63.21; H, 3.31; neut. equiv., 188.

The large clusters, m. p. 197° (dec.), 7.0 g., were *o*-phthalic acid.

3-Methylenephthalide.—*o*-Acetobenzoic acid, 3.28 g. (0.02 mole), and 5.0 ml. of acetyl chloride were refluxed gently for one and one-half hours. An external bath temperature of 50° was maintained while the excess acetyl chloride was removed under reduced pressure. The oily residue was treated with 10 ml. of water and enough 10% aqueous ammonia to make the mixture alkaline to litmus. At this point the oil had partially solidified. The mixture was extracted with ether and the ether extracts dried over anhydrous sodium sulfate. The ether was distilled *in vacuo* leaving a semi-solid residue, 2.2 g. This was dissolved in 4.0 ml. of acetone, centrifuged and the clear acetone solution decanted. When diluted with 10 ml. of water an oil separated and soon solidified, 1.5 g., m. p. 50–55°. It was sublimed at 1–2 mm. with a bath at 45–50° and 0.65 g., m. p. 57°, of product was obtained. Gabriel[2] reported a m. p. of 58–60°. The sublimed material could be crystallized from hexane.

Anal. Calcd. for $C_9H_6O_2$: C, 73.97; H, 4.11. Found: C, 73.38; H, 4.21.

The aqueous ammoniacal solution was evaporated to dryness. From the residue there was obtained 0.5 g. of *o*-acetobenzoic acid.

The yield of 3-methylenephthalide was 26.2%.

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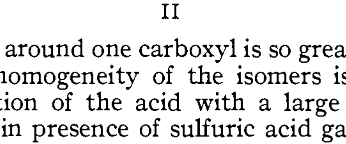
COMMUNICATIONS TO THE EDITOR

REARRANGEMENT IN PREPARATION OF ESTER ACID CHLORIDES

Sir:

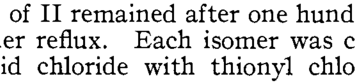
In conversion of the half ester of a dibasic acid to the ester acid chloride, it has been assumed that the chlorine becomes attached to the carbon originally present as carboxyl. Thus, Bardhan[1] prepared acid chlorides from the two half esters of trimethylsuccinic acid, and treated each with methylzinc iodide. In each case there was obtained a "similar" mixture of ethyl α,α,β-trimethyllevulinate and ethyl α,β,β-trimethyllevulinate. This was ascribed to the half esters used as starting materials being a similar mixture of isomers, in spite of convincing evidence[2] that half esters so obtained are largely a single isomer.

We have obtained the isomeric half esters, I and II, of α-butyl-α-ethylglutaric acid.[3] Here the



$$\mathrm{HO_2C{-}CH_2{-}CH_2{-}\overset{C_4H_9}{\underset{C_2H_5}{C}}{-}CO_2CH_3}$$

I

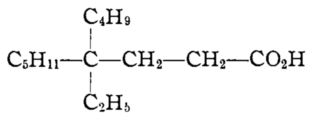


$$\mathrm{CH_3O_2C{-}CH_2{-}CH_2{-}\overset{C_4H_9}{\underset{C_2H_5}{C}}{-}CO_2H}$$

II

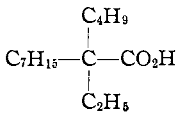
hindrance around one carboxyl is so great that the essential homogeneity of the isomers is assured. Esterification of the acid with a large excess of methanol in presence of sulfuric acid gave a high yield of II after one hour under reflux, whereas a 10% yield of II remained after one hundred forty hours under reflux. Each isomer was converted to the acid chloride with thionyl chloride and these heated with tribromoaniline in xylene. From each isomer was obtained a poor yield of a tribromoanilide, m. p. 127–128°, no depression on mixing the two. *Anal.* Calcd. for $C_{18}H_{24}NO_3Br_3$: C, 39.88; H, 4.45. Found: C, 39.94; H, 4.50. Thus, a mixture of ester acid chlorides must have been obtained from each isomer, and there was isolated only the tribromoanilide resulting from reaction with the unhindered acid chloride.

Further, the acid chloride from each isomeric half ester was treated with dibutylcadmium,[4] and the resulting mixture of keto esters was reduced by the modified Wolff–Kishner procedure.[5] There was obtained in the two cases nearly identical mixtures of acids of the expected equivalent weight and b. p. 148.5–149.5° (1.5 mm.). This mixture was separated into the acids, III (*ca.* 25%) and IV



$$\mathrm{C_5H_{11}{-}\overset{C_4H_9}{\underset{C_2H_5}{C}}{-}CH_2{-}CH_2{-}CO_2H}$$

III



$$\mathrm{C_7H_{15}{-}\overset{C_4H_9}{\underset{C_2H_5}{C}}{-}CO_2H}$$

IV

(*ca.* 75%), by virtue of the rapid esterification of III and the very slow esterification of IV. When the esterification procedure used was repeated on the residual IV, no ester was detected. *Anal.* Calcd. for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48; eq. wt., 242.4. Found for III: C, 74.09; H, 12.39; eq. wt., 245.7. Found for IV: C, 74.17; H, 12.01; eq. wt., 241.5; $n^{27}\mathrm{D}$ for III, 1.4533; for IV, 1.4472. *p*-Bromoanilide of III, m. p. 88.5–89.0°; of IV, m. p. 121.5–122°. *Anal.* Calcd. for $C_{21}H_{34}NOBr$: C, 63.62; H, 8.65. Found for deriv. of III: C, 64.11; H, 8.42. Found for deriv. of IV: C, 63.51; H, 8.72.

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(1) Bardhan, *J. Chem. Soc.*, 2604 (1928).

(2) Bone, Sudborough and Sprankling, *ibid.*, **85**, 534 (1904).

(3) Bruson and Riener, THIS JOURNAL, **66**, 56 (1944).

(4) Cason, *ibid.*, **68**, 2078 (1946).

(5) Huang-Minlon, *ibid.*, **68**, 2487 (1946).