thallium is 147°, and distillation should be carried out at reduced pressure to avoid explosive decomposition. Some other physical, and some chemical properties are described.

AMES, IOWA. RECEIVED[14] DECEMBER 31, 1945

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[14] Original manuscript received November 16, 1942.

NOTES

Iodinated Dialkylaminoalkyl Pyridyl Ethers

BY ALFRED BURGER AND MARIE S. BAILEY

The substitution of the hydroxypyridine for hydroxyphenyl groups in halogenated derivatives of these ring systems has proved a valuable lead in improving bactericidal properties in a number of cases. We hoped, therefore, that replacement of the benzene ring in certain tuberculostatic halogenated dialkylaminoalkyl phenyl ethers[1] by pyridine would produce more highly active compounds. The few examples reported below did not support this expectation; none of the derivatives was tuberculostatic *in vitro*. An analogous basic ether of 5,7-diiodo-8-hydroxyquinoline, as well as 2,5-diiodo-6-hydroxy-nicotinic acid were also inactive.

Experimental

Diiodo-3-hydroxypyridine and triiodo-3-hydroxypyridine were prepared by the method of Binz and Maier-Bode.[2] Both phenols were methylated with diazomethane in ether–methanol solution.

Diiodo-3-methoxypyridine, obtained as colorless shiny crystals in a yield of 90%, melted at 100.5–101°.

Anal. Calcd. for $C_6H_5I_2NO$: N, 3.88. Found: N, 3.88.

Triiodo-3-methoxypyridine crystallized from dilute methanol as colorless, shiny needles, m. p. 113°. The yield was 99%.

Anal. Calcd. for $C_6H_4I_3NO$: N, 2.89. Found: N, 2.73.

2,5-Diiodo-6-hydroxynicotinic Acid.—A solution of 8.15 g. of iodine and 9 g. of potassium iodide in 20 cc. of water was added dropwise to a hot mechanically stirred solution of 10 g. of 6-hydroxynicotinic acid[3] in 125 cc. of 20% ammonium hydroxide. The reaction mixture was filtered from a greenish precipitate, and the filtrate acidified with acetic acid. The resulting brown precipitate was recrystallized three times from a 1:1 mixture of dioxane and ethanol. The shiny yellow needles melted at 242–249° (dec.).

Anal. Calcd. for $C_6H_3I_2NO_3$: N, 3.57. Found: N, 3.82.

Diiodo-3-(2-diethylaminoethoxy)-pyridine.—One and eight-tenths grams of diiodo-3-hydroxypyridine was dissolved in a mechanically stirred solution of 0.07 g. of sodium in 20 cc. of methanol. A solution of diethylaminoethyl chloride, prepared by dissolving 1 g. of diethylaminoethyl chloride hydrochloride in a solution of 0.1 g. of sodium in 10 cc. of methanol, was added, and the mixture refluxed for eighteen hours. The solvent was removed under reduced pressure, the oil dissolved in 75 cc. of ether, and washed with two 35-cc. portions of dilute sodium hydroxide solution and then with water. The ether solution was dried over anhydrous sodium sulfate, the ether distilled, and the residual oil converted to its dihydrochloride in acetone solution. Two recrystallizations from methanol furnished a colorless salt of m. p. 204–205°. The yield was 0.7 g. (26%).

Anal. Calcd. for $C_{11}H_{16}I_2N_2O \cdot 2HCl$: N, 5.40. Found: N, 5.50.

Diiodo-3-[(2-methylpiperidino)-3-propoxy]-pyridine Dihydrochloride was prepared in an analogous manner, using a 30% excess of 3-(2-methylpiperidino)-propyl chloride hydrochloride, and the corresponding amounts of the other reagents. The salt, obtained in a yield of 31% after crystallization from methanol, melted at 129–129.5°.

Anal. Calcd. for $C_{14}H_{20}I_2N_2O \cdot 2HCl$: N, 5.08. Found: N, 5.23.

5,7-Diiodo-8-[3-(2-methylpiperidino)-propoxy]-quinoline.—To a mechanically stirred solution of 0.6 g. of sodium in 20 cc. of methanol and 100 cc. of dioxane was added 5 g. of 5,7-diiodo-8-hydroxyquinoline and 3.25 g. of 3-(2-methylpiperidino)-propyl chloride. After boiling under reflux for nine hours, the mixture was worked up in the customary manner. The dihydrochloride crystallized from benzene and melted at 127–128.5°. The yield was 0.9 g. (11.4%).

Anal. Calcd. for $C_{18}H_{22}I_2N_2O \cdot 2HCl$: N, 4.59. Found: N, 4.58.

The authors are grateful to Eli Lilly and Company for a Fellowship.

UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VIRGINIA RECEIVED OCTOBER 22, 1945

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[1] Burger, Wilson, Brindley and Bernheim, THIS JOURNAL, **67**, 1416 (1945).

[2] Binz and Maier-Bode, *Z. angew. Chem.*, **49**, 486 (1936).

[3] We are indebted to Dr. W. A. Lott for this material.

The Intermetallic Compound $Mg_4Na_4Pb_3$

BY GEORGE CALINGAERT, HYMIN SHAPIRO AND IVAR T. KROHN

In the course of a thermal investigation of the ternary system Mg–Na–Pb, the alloy $Mg_4Na_4Pb_3$ was found to be a compound with an open maximum. Melts were made in 200-g. batches under an atmosphere of nitrogen in a closed iron bomb fitted with a thermocouple well. The bomb was held at 725° for forty-five minutes with intermittent shaking. The alloy was then allowed to cool at the constant rate of 1° per minute, the rate of cooling being controlled by reduction of the heat input through a calibrated rheostat system. Temperature measurements were made on a Leeds and Northrup K-2 potentiometer, using thermocouples calibrated against the freezing point of lead. The cooling curves were interpreted after the manner of Tammann.[1]

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[1] Tammann, "A Textbook of Metallography," The Chemical Catalog Co., Inc., New York, 1925, p. 181.

Four alloys of compositions immediately surrounding the $Mg_4Na_4Pb_3$ peak in the ternary diagram were analyzed thermally in order to define the compound region; the experimental data are given below.

THERMAL ANALYSIS OF $Mg_4Na_4Pb_3$ REGION OF Mg–Na–Pb SYSTEM

Atom % [a]			Temperature breaks					
			Primary		Secondary		Tertiary	
Mg	Na	Pb	Temp., °C.	Time, min.	Temp., °C.	Time, min.	Temp., °C.	Time, min.
36.36	36.36	27.27 ($Mg_4Na_4Pb_3$)	600.7	23	383.8	<1[b]		
37.50	37.50	25.00 ($Mg_3Na_3Pb_2$)	589.8	7	559.9	7		
35.00	35.00	30.00 ($Mg_7Na_7Pb_6$)	583.0	9	476.8	3	407.9	<1[b]
34.20	39.00	26.80	596.5	16	555.2	<1[b]	350.0	<1[b]
38.30	34.00	27.70	596.9	22	531.7	<1[b]	398.9	3

[a] The metals used were Dow extruded bar magnesium of over 99.9% purity, du Pont sodium and Asarco lead of over 99.95% purity. [b] These small breaks are of doubtful validity.

The cooling curve for $Mg_4Na_4Pb_3$ showed a long, flat, sharp break at 600.7° and a very short break at 383.8°. The latter is attributed to a slight deviation from theoretical in the composition of the alloy. The four alloys surrounding the compound had lower initial breaks of shorter duration and, in all but one instance, more definite secondary breaks.

The compound $Mg_4Na_4Pb_3$ is a brittle alloy, gray in color, and of more pronounced crystallinity than the other alloys in its region. Moist air corrodes the compound rapidly. It reacts vigorously with water or acid; in the reaction with acid, the evolved hydrogen is ignited. The approximate density of the alloy is 4.5–4.7 g./cc.

The compound was difficult to polish because of rapid oxidation, even when immersed in mineral oil. Microscopic examination of a polished surface disclosed three phases, with the main phase of $Mg_4Na_4Pb_3$ present to an extent greater than 99%.

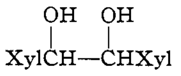
CHEMICAL RESEARCH LABORATORY
ETHYL CORPORATION
DETROIT, MICHIGAN

RECEIVED NOVEMBER 28, 1945

A Synthesis of Di-(2,4-xylyl)-acetic Acid

BY REYNOLD C. FUSON AND M. L. WARD[1]

In a search for a convenient route to di-(2,4-xylyl)-acetaldehyde and the corresponding acid an attempt was made to reduce 2,4-xylaldehyde bimolecularly and to dehydrate the resulting hydrobenzoin (I). It is interesting that this relatively unhindered aldehyde did undergo bimolecular reduction with the binary mixture, Mg-MgI_2.[2] The product proved to be a mixture of the two glycols previously reported by Law.[3] Dehydration of the hydroxyloin, however, yielded a compound which was not the desired aldehyde and which appeared to be the desoxyxyloin (II).



$$\mathrm{Xyl\overset{OH}{\underset{|}{C}}H{-}\overset{OH}{\underset{|}{C}}HXyl}$$

I

$XylCOCH_2Xyl$

II

A synthesis of the dixylylacetic acid was carried out according to the scheme

$$\mathrm{XylMgBr \xrightarrow{HCO_2C_2H_5} (Xyl)_2CHOH \longrightarrow (Xyl)_2CHCl \longrightarrow (Xyl)_2CHCN \longrightarrow (Xyl)_2CHCO_2H}$$

Experimental

Bimolecular Reduction of 2,4-Xylaldehyde.—The mixture obtained by treatment of the aldehyde with the binary mixture, Mg–MgI_2, was separated by the use of hot high-boiling petroleum ether, which dissolved the isohydroxyloin whereas the hydroxyloin was almost completely insoluble. The isohydroxyloin, after repeated recrystallization, melted at 129–130°. The hydroxyloin melted at 153–154°. A by-product was 2,4-xylic acid, m. p. 123–124°.[4]

Another by-product, isolated from the hydroxyloin fraction and crystallized from methanol, melted at 172–173°.

Anal. Calcd. for $C_{36}H_{42}O_4$: C, 80.26; H, 7.86. Found: C, 80.19; H, 8.28.

This compound was a bimolecular derivative and appeared to be a glycol; it formed an **acetate**, which after recrystallization from methanol melted at 126–127°.

Anal. Calcd. for $C_{44}H_{50}O_8$: C, 74.76; H, 7.13. Found: C, 74.71; H, 7.55.

The **acetate** of the hydroxyloin, purified by recrystallization from methanol, melted at 105–106°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.75; H, 7.39.

Reduction of Hydro-2,4-xyloin. (a) With Phosphorus and Iodine.—A mixture of 0.2 g. of hydro-2,4-xyloin, 0.3 g. of iodine, 0.6 g. of red phosphorus and 30 ml. of glacial acetic acid was heated under reflux for twenty-four hours and poured into water containing a small amount of sodium sulfite. The **1,2-di-(2,4-xylyl)-ethylene**, isolated by conventional methods, was recrystallized from methanol; m. p. 108–109.5°.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.48; H, 8.73.

(b) With Hydrogen Iodide.—A mixture of 0.3 g. of hydro-2,4-xyloin, 40 ml. of glacial acetic acid and 10 ml. of hydriodic acid (sp. gr. 1.50) was heated on a steam-bath for twelve hours. The solution developed a deep red color and droplets of oil appeared on the surface. The mixture was poured into water and the organic product taken up in ether. The **1,2-di-(2,4-xylyl)-ethane**, remaining after removal of the solvent by distillation, was purified by recrystallization from methanol; m. p. 71–72°.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.69; H, 9.31. Found: C, 90.86; H, 9.23.

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[1] Abbott Fellow, 1941–1942.

[2] Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927); **52**, 4967 (1930).

[3] Law, *J. Chem. Soc.*, 748 (1907).

[4] Auwers and Kockritz, *Ann.*, **352**, 288 (1907).

Dehydration of Hydro-2,4-xyloin

(a) **With Sulfuric Acid.**—A mixture of 1 g. of the hydroxyloin, 60 ml. of concentrated sulfuric acid, and 45 ml. of water was heated in a steam-bath for forty-five minutes. The product was purified by recrystallization from methanol; m. p. 145–146°.

Anal. Calcd. for $C_{36}H_{40}O_2$: C, 85.67; H, 7.99; mol. wt., 536. Found: C, 85.85; H, 8.29; mol. wt. (ebullioscopic in chloroform), 460, 512.

A Zerewitinoff determination showed that the compound had no active hydrogen. It is probably the tetraxylyldioxane.

A mixture of 1 g. of this compound, 50 ml. of glacial acetic acid and 15 ml. of hydriodic acid (sp. gr. 1.50) was heated for four hours on the steam-bath. By suitable manipulation the product was resolved into two solids. One, after being recrystallized from methanol, melted at 201–203°.

Anal. Calcd. for $C_{36}H_{42}$: C, 91.08; H, 8.92. Found: C, 91.06; H, 8.71.

The other solid melted at 70–71° after repeated recrystallization from methanol.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.69; H, 9.31. Found: C, 90.86; H, 9.23.

These two compounds were not examined further.

(b) **With a Mixture of Acetic and Hydrochloric Acids.**—A mixture of 1 g. of the hydroxyloin, 24 ml. of glacial acetic acid and 6 ml. of concentrated hydrochloric acid was heated under reflux for four hours. The product was crystallized from glacial acetic acid; m. p. 53–54°.

Anal. Calcd. for $C_{18}H_{22}O$: C, 85.67; H, 7.99. Found: C, 85.39; H, 7.67.

This compound failed to form an acetate or benzoate and appeared to be the desoxy-2,4-xyloin.

Di-(2,4-xylyl)-methyl Ether.—An attempt was made to prepare di-(2,4-xylyl)-carbinol by adding 21.4 g. of ethyl formate to a two-fold excess of 2,4-xylylmagnesium bromide. The chief product, isolated by conventional procedures, was 17 g. of **di-(2,4-vinyl)-methyl ether** melting at 180–185°. After recrystallization from isopropyl alcohol it melted at 184–185.5°.

Anal. Calcd. for $C_{34}H_{39}O$: C, 88.26; H, 8.28. Found: C, 88.21; H, 8.38.

A viscous oil was isolated also. Although it failed to crystallize, it gave the reaction expected of the **di-(2,4-xylyl)-carbinol**. Coops, Nauta, Ernsting and Faber[5] reported a melting point of 101° for this compound. When 20 g. of this oil was treated with concentrated hydrochloric acid according to the procedure of Reid[6] for di-(*o*-tolyl)-methyl chloride, a 70% yield of **di-(2,4-xylyl)-methyl chloride** was obtained, m. p. 85–88°. The chloride was recrystallized from low-boiling petroleum ether; m. p. 85–86°.[5]

The chloride was made from the dixylylmethyl ether in a similar manner; yield 63%.

Di-(2,4-xylyl)-acetonitrile.—The procedure was similar to that used by Newman[7] in the preparation of α-naphthonitrile. A mixture of 8.5 g. of di-(2,4-xylyl)-methyl chloride, 3.54 g. of cuprous cyanide and 5 ml. of pyridine (dried over calcium oxide) was heated at 240–250° for twenty-four hours. The nitrile weighed 6.9 g. and melted at 110–113°. It was recrystallized from methanol; m. p. 112–113.5°.

Anal. Calcd. for $C_{18}H_{18}N$: C, 86.69; H, 7.68. Found: C, 86.97; H, 7.63.

Di-(2,4-xylyl)-acetic Acid.—A mixture of 2 g. of di-(2,4-xylyl)-acetonitrile, 6 g. of potassium hydroxide, 1 ml. of water and 60 ml. of diethylene glycol was heated under reflux for four hours. The acid, isolated in the usual way, was recrystallized from a mixture of benzene and low-boiling petroleum ether; m. p. 181–182°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.71; H, 7.75.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
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RECEIVED NOVEMBER 23, 1945

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(5) Coops, Nauta, Ernsting and Faber, *Rec. trav. chim.*, **59**, 1109 (1940).

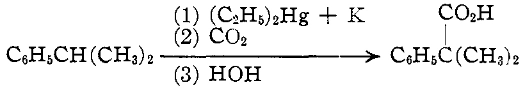
(6) Reid, THIS JOURNAL, **61**, 3238 (1939).

(7) Newman, "Organic Syntheses," **21**, 89 (1941).

Metalation of Cumene by Ethylpotassium[1]

BY HENRY GILMAN AND LEO TOLMAN

The metalation of cumene by ethylpotassium (prepared *in situ* from diethylmercury and potassium) proceeds laterally to some extent. This was established by carbonation of the metalation products and isolation of phenyldimethylacetic acid. The reference sample of phenyldimethylacetic acid was prepared in accordance with the procedure of Ziegler and co-workers[2] by carbonation of the product obtained from the cleavage of 2-phenyl-isopropyl methyl ether with sodium–potassium alloy.



$$C_6H_5CH(CH_3)_2 \xrightarrow[\text{(3) HOH}]{\text{(1) }(C_2H_5)_2Hg + K\text{ (2) }CO_2} C_6H_5\overset{\overset{\displaystyle CO_2H}{|}}{C}(CH_3)_2$$

On the basis of a recent report by Morton and co-workers[3] on the metalation of cumene by amylsodium it is possible that some of the unidentified acids in the carbonation mixture may contain the *o*- and *p*-isopropylbenzoic acids. In this connection, we have observed that the *p*-isopropylbenzoic acid can be conveniently prepared in 49% yield by carbonation of *p*-isopropylmagnesium bromide.

Experimental

A mixture of 2.6 g. (0.01 mole) of diethylmercury, 1.37 g. (0.035 g. atom) of potassium and 25 cc. of cumene was stirred at room temperature, in an atmosphere of dry nitrogen, for ten hours. The mixture was then carbonated by Dry Ice, and the base-soluble material was precipitated from a dilute basic solution by the addition of hydrochloric acid. Fractional crystallization of the crude acid mixture from petroleum ether (b. p. 60–68°) first gave 0.3 g. (19%) of acid melting at 65–68°. Further recrystallization yielded 0.15 g. of an acid melting at 76–77°. This acid was shown, by the method of mixed melting points, to be identical with phenyldimethylacetic acid prepared in 58% by Ziegler's[2] procedure.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA
RECEIVED NOVEMBER 5, 1945

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(1) Paper LXIII in the series "The Relative Reactivities of Organometallic Compounds." The preceding paper with Jones is in *J. Org. Chem.*, **10**, 505 (1945).

(2) Ziegler and Theilmann, *Ber.*, **56**, 1740 (1923); Ziegler, Crössmann, Kleiner and Schäfer, *Ann.*, **473**, 1 (1929).

(3) Morton, Massengale and Brown, THIS JOURNAL, **67**, 1620 (1945).

Flocculation of Suspensions by Immiscible Liquids

BY EARL K. FISCHER, EDMUND N. HARVEY, JR., AND AGNES S. DYER

The mechanism of the flocculation of solid particles dispersed in water-immiscible liquids has long been the subject of theoretical and experimental investigation. Evidence has accumulated showing that water and surface-active substances added to such solid-in-liquid dispersions profoundly modify the extent of flocculation as evidenced by sedimentation volumes[1,2,3,4] and plastic-flow properties.[4,5]

A recent study by Kruyt and Van Selms[6] on the plasticity of starch, quartz and glass bead suspensions in organic media as influenced by added water came to the attention of the authors while work indicating similar conclusions was in progress in this Laboratory. Experiments involving different systems with added liquids other than water are reported briefly in this note pending a more detailed investigation.

A thoroughly dried powder of "hydrophilic" surface properties, such as titanium dioxide, may be dispersed in a non-polar hydrocarbon oil and maintained in a deflocculated state provided the system is kept free of moisture. It was observed that immiscible polar compounds other than water, when added in small relative quantities, cause flocculation of the dispersed particles. Experiments showed marked differences in the extent of flocculation with different liquids. It was inferred that the immiscible reagent formed a bridge between adjacent particles and that the force necessary to separate the solid particles would be essentially that required to increase the liquid–liquid interface so formed. The tension at the interface between reagent and suspending liquid should, therefore, be related to the extent of flocculation which is measurable as the yield value of a bulk dispersion in a rotational viscometer.

In these experiments, titanium dioxide of a "water-dispersible" pigment grade was dried for ten days at 110° and ground on a three-roll mill in a mixture of equal parts by weight of a pharmaceutical mineral oil and isobutylene polymer to give a solids content of 30% by weight. The particle size (d_3) of the pigment was 0.18 μ as calculated from adsorption measurements with nitrogen at $-198°$ by the Brunauer–Emmett–Teller procedure. The viscosity of the oil mixture was 13.6 poises at 30°. Flocculating reagents (see caption to Fig. 1) were mixed with portions of this dispersion and the plastic viscosity and yield values were measured in absolute units on a rotational viscometer.[7] Interfacial tension measurements of the various added reagents against the dispersion medium were made on a Cenco–du Nouy tensiometer at 30°.

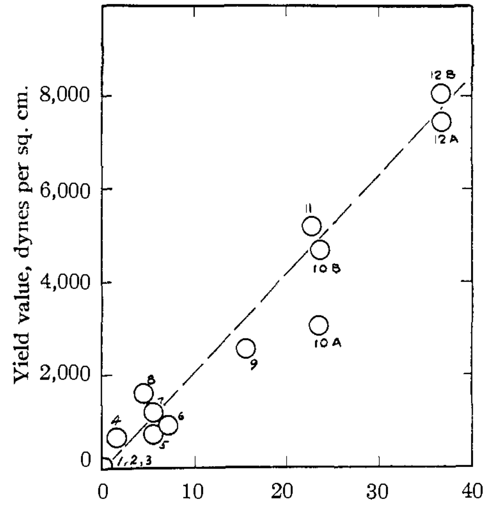

Fig. 1.—Variation of yield value of titanium dioxide-non-polar oil suspensions on addition of polar liquids: 1, control (no reagent); 2, octyl alcohol, 1.2%; 3, 2-ethylbutyl alcohol, 1.0%; 4, propyl alcohol, 3%; 5, 2,3-butanediol, 3%; 6, furfuryl alcohol, 3%; 7, methanol, 3%; 8, ethanol, 3%; 9, ethylene glycol, 3%; 10, glycerol, A, 2.2%, B, 0.6%; 11, formamide, 2.0%; 12, water, A, 0.6%, B, 1.4%. Water content calculated to form unimolecular film, 0.26%. (All percentages by weight on dispersed phase; all measurements made at 30°.)

The curve (Fig. 1) shows the unmistakable upward trend of yield value with increasing interfacial tension as predicted, despite difficulties in maintaining anhydrous conditions and in preventing evaporation of appreciably volatile reagents during experimental manipulation.

These experiments indicate that rigorous drying or removal of contaminants would serve to reduce the numerous cases of flocculation attributed to "poor wetting" of a solid surface by a liquid. Further, the plotted data suggest that surface-active agents promote deflocculation (and hence increase the mobility) of a solid–liquid system by lowering the liquid-liquid interfacial tension, thus weakening or removing the bridge between particles. In the opposite case, that of a solid with hydrophobic surface properties dispersed in a water-miscible liquid, the addition of a substance immiscible with the suspending liquid increases the extent of flocculation, as is implicit in several previously reported experiments[5] showing that certain reagents may increase the yield value of solid-in-liquid suspensions.

INTERCHEMICAL CORPORATION
RESEARCH LABORATORIES
NEW YORK 19, NEW YORK
RECEIVED JUNE 8, 1945

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(1) W. D. Harkins and D. M. Gans, *J. Phys. Chem.*, **36**, 86–97 (1932).

(2) L. W. Ryan, W. D. Harkins and D. M. Gans, *Ind. Eng. Chem.*, **24**, 1288–1298 (1932).

(3) C. R. Bloomquist and R. S. Shutt, *Ind. Eng. Chem.*, **32**, 827–831 (1940).

(4) W. Gallay and I. E. Puddington, *Can. J. Research*, **B21**, 171–178 (1943).

(5) E. K. Fischer and C. W. Jerome, *Ind. Eng. Chem.*, **35**, 336–43 (1943).

(6) H. R. Kruyt and F. G. Van Selms, *Rec. Trav. Chim.*, **62**, 398–426 (1943).

(7) H. Green, *Ind. Eng. Chem., Anal. Ed.*, **14**, 576–585 (1942).

The Comparison of Zirconium Tetrachloride with Aluminum Chloride as a Friedel–Crafts Catalyst

BY H. W. HEINE,[1] D. L. COTTLE AND H. L. VAN MATER

The recent availability of zirconium tetrachloride in commercial quantities has prompted the investigation of this material as a catalyst for the synthesis of ketones according to Friedel and Crafts. Krishnamurti has previously reported[2] zirconium tetrachloride to be effective in the preparation of the ketones acetophenone and benzophenone.

We have conducted a preliminary comparison of zirconium tetrachloride with aluminum chloride by measuring the yields of *p*-methyl-acetophenone from acetyl chloride and toluene. The procedure and analytical method used in this investigation were essentially those developed by Dermer and co-workers.[3,4]

The yields of ketone obtained with zirconium tetrachloride and aluminum chloride are set forth in the accompanying graph. It will be seen that the results with zirconium tetrachloride are at once better but less consistent than those obtained with aluminum chloride. No explanation is offered for the erratic behavior of zirconium tetrachloride.

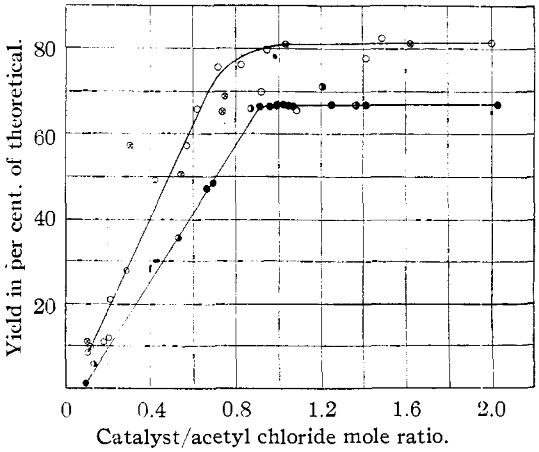

Fig. 1—Variation of yield of *p*-methylacetophenone with mole ratio of catalyst/acetyl chloride: ●, $AlCl_3$ at 100°; ◑, $AlCl_3$ at room temp.; ○, $ZrCl_4$ at 100°; ⊕, $ZrCl_4$ at room temp.

Macro runs in which the *p*-methylacetophenone was actually isolated and weighed gave essentially the yields predicted by the semi-micro method of Dermer. In these macro runs very efficient stirring was found necessary; no stirring was used in the micro runs.

The investigation is being continued.

Experimental

Reagents.—Eastman Kodak Co. toluene and Merck acetyl chloride were used.

Zirconium tetrachloride was obtained from the Titanium Alloy Manufacturing Company and anhydrous sublimed technical aluminum chloride was purchased from Eimer and Amend. All of the above reagents were used without further purification.

Procedure.—The modifications to the original procedure of Dermer adopted by Dermer and Billmeier[4] were used in this investigation. The time of reaction for all experiments heated at 100° was one hour. For all experiments carried out at room temperature, the time of reaction was two hours.

RUTGERS UNIVERSITY
NEW BRUNSWICK, N. J. RECEIVED NOVEMBER 17, 1945

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[1] Holder of the William F. Meredith Fellowship, sponsored by Titanium Alloy Manufacturing Company, Niagara Falls, N. Y.

[2] P. Krishnamurti, *J. Madras Agr. Students Union*, **40** (1928).

[3] O. C. Dermer, David M. Wilson, F. M. Johnson and V. H. Dermer, THIS JOURNAL, **63**, 2881 (1941).

[4] O. C. Dermer and Robert Billmeier, *ibid.*, **64**, 464 (1942).

Sodium Hydrogen Citrates

BY DAVID I. HITCHCOCK

Primary and secondary sodium citrates were described long ago by Heldt[1] and by Salzer,[2] but their analytical data are hardly adequate to prove that the salts were pure substances. No recent account of the preparation and analysis of acid sodium citrates has been found, and they are not listed in available catalogs of pure chemicals. Because of the possible use of these salts for the preparation of buffers and for the preservation of blood,[3] it seemed worth while to re-investigate their preparation and composition.

It was found that microscopic crystals of either salt could be obtained from aqueous solutions containing approximately the calculated proportions of acid and alkali, but that the crystals did not have the theoretical ratios of sodium to acid hydrogen unless the composition of the solutions was very carefully controlled. Preparations which contained a 1 to 4% excess of acid or base could be purified by one or two recrystallizations from water.

Pure salts were obtained without recrystallization by preparing the solutions from anhydrous citric acid, dried at 70°, and anhydrous sodium carbonate, dried at 160°. One-mole portions of the acid were dissolved in 600 ml. of water, and the calculated amounts of carbonate were added in small portions, with stirring. The solutions were boiled for half an hour, filtered into weighed evaporating dishes, and concentrated on a steam-bath until the remaining water weighed 75 to 85% as much as the dry salt. Cooling to 20 or 10° yielded pastes of microscopic crystals; the disodium salt had the form of square needles or rectangular prisms, while the crystals of the monosodium salt appeared to be nearly perfect cubes. After filtration with suction, small filtrates containing about 25% of the materials were discarded. The crystals were air-dried, ground to pass a 20-mesh sieve, and dried at 70°.

Acid hydrogen was determined by titration with 0.1 *M* sodium hydroxide, free from carbonate, standardized against potassium hydrogen phthalate. The end-point chosen for the titrations was *p*H 9.2, as estimated by means of phenolphthalein indicator and a comparison solution of pure borax. Sodium was determined by conversion to the sulfate. Because of the large amounts of gas evolved in the decomposition of citrates by sulfuric acid, it was necessary to increase the temperature very gradu-

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[1] W. Heldt, *Ann.*, **47**, 157 (1843).

[2] Th. Salzer, *Arch. Pharm.*, **229**, 547 (1891); **231**, 514 (1893).

[3] J. F. Loutit and P. L. Mollison, *Brit. Med. J.*, **1943**, II, 744.

ally; periods of a day or night at 110, 320 and 540° were adequate when followed by ten-minute heatings to constant weight at about 800°. These analyses showed that the ratio of sodium to acid hydrogen was 0.500 ± 0.001 for the monosodium salt, and 2.002 ± 0.001 for the disodium salt. The analyses also indicated a formula weight of 215.4 for the monosodium salt and 263.5 for the disodium salt. The former figure is somewhat more than 214.1, the formula weight of anhydrous monosodium citrate, while the latter figure indicates that the disodium salt contained 1.5 moles of water, which would make the calculated value 263.1. The air-dried preparations of both salts lost less than 0.5% in weight at 70 or 110°, and also remained constant in weight when kept over a saturated sodium chloride solution at room temperature. The monosodium salt became caked on standing in a stoppered bottle, but titration of the caked material did not reveal any absorption of moisture. The disodium salt could be dried more rapidly after washing with 95% alcohol, which did not remove the 1.5 moles of water. Alcohol withdrew a little acid from the monosodium salt. None of the preparations of either salt had the composition of the monohydrates reported by Heldt[1] and Salzer.[2]

These acid citrates differ from many other acid salts, such as the phosphates, in one important respect. Either of the acid citrates by itself forms a well buffered solution in water. The following *p*H values were obtained for 0.1 and 0.01 *M* solutions at 25°: monosodium citrate, 3.70 and 3.88; disodium citrate, 4.96 and 5.30, respectively. These values, which were checked within 0.003 *p*H with solutions made from three different preparations of each salt, were obtained by means of a carefully tested glass electrode in a water-jacketed cell with liquid junction, similar to that described in a previous paper.[4] They are based on a *p*H value of 4.008 for 0.05 *M* potassium acid phthalate.

Reliable solutions may also be obtained, without isolating the acid salts, from carefully standardized solutions of citric acid and sodium hydroxide, according to Sörensen.[5]

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[4] D. I. Hitchcock and A. C. Taylor, This Journal, **59**, 1812 (1937).

[5] S. P. L. Sörensen, *Biochem. Z.*, **21**, 131 (1909).

Laboratory of Physiology
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Received December 5, 1945

Studies on the Willgerodt Reaction. I. Some Extensions of the Reaction

By John A. King and Freeman H. McMillan

Nearly sixty years ago Willgerodt[1,2] discovered the reaction which has come to bear his name: treatment of an aliphatic aromatic ketone with yellow ammonium sulfide at a moderately high temperature in a sealed tube to effect the transformation of the ketone to an aralkyl amide. Until Cavalieri, Pattison and Carmack[3] announced, last October, their application of the reaction to purely aliphatic and to alicyclic–aliphatic ketones, the assumption had always been implied that the reaction was confined to aromatic–aliphatic ketones. We have likewise found that this assumed restriction does not exist.

$$C_6H_5COCH_3 \xrightarrow{(NH_4)_2S_x} C_6H_5CH_2CONH_2$$

When phenylacetone was treated with yellow ammonium sulfide under the same conditions as used by Willgerodt and Merk[4] for propiophenone the product was β-phenylpropionamide.

$$C_6H_5CH_2COCH_3 \xrightarrow{(NH_4)_2S_x}$$

$$C_6H_5CH_2CH_2CONH_2 \xleftarrow{(NH_4)_2S_x} C_6H_5COCH_2CH_3$$

After it was thus shown that the carbonyl group of the ketone did not need to be adjacent to the aromatic ring for the reaction to occur, it seemed of interest to determine if compounds of the next lower state of oxidation would undergo the reaction. It was found that both phenylmethylcarbinol and its dehydration product, styrene, gave phenylacetamide in approximately the same yield as did acetophenone, under the conditions of Willgerodt and Merk.[4]

$$\begin{tikzcd}
C_6H_5COCH_3 \arrow[dr] & C_6H_5CHOHCH_3 \arrow[d] & C_6H_5CH{=}CH_2 \arrow[dl] \\
& C_6H_5CH_2CONH_2 &
\end{tikzcd}$$

Work on this reaction is being continued.

Experimental[5]

Yellow ammonium sulfide was prepared according to the directions of Willgerodt and Merk. Concentrated ammonium hydroxide (200 cc.) was saturated at room temperature with hydrogen sulfide. To the solution, which weighed 244 g., there was added 24.4 g. of sulfur, which was stirred into solution.

Phenylacetone was prepared by the method used by Baker[6] for 1-anisyl-2-butanone. The same material was also prepared much more easily by the method of Magidson and Garkusha.[7] When the preparation was carried out on a scale four times as large as reported by Magidson and Garkusha there was obtained, in addition to phenylacetone, b. p. 88–92° (6 mm.), 37 g. of a fraction, b. p. 171–179° (6 mm.), which gave an oxime, m. p. 119–122°. The oxime of *s*-diphenylacetone is variously reported[8] to melt from 118 to 125°.

Phenylmethylcarbinol was prepared by aluminum isopropoxide reduction of acetophenone, by the procedure of Lund[9]; the product boiled at 77–81° (5 mm.).

The styrene used was Eastman Kodak Co. White Label material.

Phenylacetone and Ammonium Polysulfide.—Phenylacetone (3.0 g.) and ammonium polysulfide (15 g.) were heated for five hours at 210 ± 5° in a pressure tube.[10] The solid material removed from the tube weighed 2.0 g. (60% crude) and melted at 86–89°; two recrystallizations of the material from water raised its melting point to 101.5°. When it was mixed with an authentic sample of

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[1] Willgerodt, *Ber.*, **20**, 2467 (1887).

[2] Willgerodt, *ibid.*, **21**, 534 (1888).

[3] Cavalieri, Pattison and Carmack, This Journal, **67**, 1783 (1945).

[4] Willgerodt and Merk, *J. prakt. Chem.*, [2] **80**, 192 (1909).

[5] Melting points and boiling points are uncorrected.

[6] Baker, This Journal, **65**, 1576 (1943).

[7] Magidson and Garkusha, *J. Gen. Chem.*, *U. S. S. R.*, 11, 339 (1941); *C. A.*, **35**, 5868 (1941).

[8] Beilstein, "Handbuch der organischen Chemie," 4th ed., **7**, 446 (1925); First Supplement, **7–8**, 238 (1931).

[9] Lund, *Ber.*, **70B**, 1520 (1937).

[10] The tube used was of a design suggested by Dr. J. S. Buck, Associate Director of Chemical Research of these Laboratories. An ordinary 13-inch Pyrex Carius tube was drawn down on the open end and had sealed to it an 8-inch length of 10-mm. OD-5 mm. ID Pyrex tubing. After the tube was filled the smaller tube was sealed on the end. A pressure tube of this type can be used six or eight times before another length of the smaller tubing needs to be sealed on and can be used a great many times, as contrasted with the ordinary Carius tube which has a relatively short life.

β-phenylpropionamide,[11] m. p. 100–100.5°, the mixture melted at 100.5–101°.

Phenylmethylcarbinol and Ammonium Polysulfide.—Phenylmethylcarbinol (3.0 g.) and ammonium polysulfide (15 g.) were heated four hours at 210 ± 5° in a pressure tube. The solid material was removed by filtration and the mother liquor was extracted with ether from which there was obtained more of the product. The crude product (wt. 1.6 g., 48% yield, crude) was recrystallized once from water to give white plates, m. p. 156.5–157°, undepressed when mixed with an authentic sample of phenylacetamide.

Styrene and Ammonium Polysulfide.—Styrene (3.0 g.) and ammonium polysulfide (15 g.) were heated four hours at 210 ± 5° in a pressure tube. The crude product, isolated as above, weighed 1.64 g. (49% yield, crude); after recrystallization from water it melted at 156–157°, undepressed when mixed with an authentic sample of phenylacetamide.

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[11] Conrad, *Ann.*, **204**, 174 (1880); Hofmann, *Ber.*, **18**, 2740 (1885).

RESEARCH LABORATORIES
WINTHROP CHEMICAL COMPANY, INC.
RENSSELAER, NEW YORK
RECEIVED AUGUST 23, 1945

Preparation of 6-Methylpyrazine-2-carboxylic Acid

BY FREDERICK LEONARD AND PAUL E. SPOERRI

In the course of our studies on pyrazine carboxylic acids it was of interest to prepare the 6-methylpyrazine-2-carboxylic acid. The related acid, 5-methylpyrazine-2,3-dicarboxylic acid, obtained by the oxidation of 2-methylquinoxaline had been described by Böttcher in 1913.[1] By considerable modification of Böttcher's oxidation procedure, followed by decarboxylation, we have been able to prepare the desired 6-methylpyrazine-2-carboxylic acid in satisfactory yields.

The mono carboxylic acid melted sharply at 138° with decomposition. Since Stoehr[2] found that 5-methylpyrazine-2-carboxylic acid melts at 200°, the substance we obtained can only be the isomeric 6-methylpyrazine-2-carboxylic acid.

Experimental

5-Methylpyrazine-2,3-dicarboxylic Acid.—Twenty-eight and eight-tenths grams of 2-methylquinoxaline was dissolved in 2400 cc. of water containing 8 g. of potassium hydroxide. To this solution at 50°, a solution of 176 g. of potassium permanganate in 1600 cc. of water, preheated to 50°, was added dropwise with good stirring. The addition took about two and one-half hours. The mixture was heated for an additional hour, 50 cc. of alcohol was added and heating continued for a half hour more. The filtrate from the manganese dioxide was concentrated to about 1 liter, made alkaline with concentrated ammonia, and a solution of 142 g. of calcium nitrate tetrahydrate in 200 cc. of water added. After the mixture had been digested on a steam-bath for one hour, the calcium oxalate was filtered off and washed with water. The combined filtrate and washings were made acid to congo red with 1:1 nitric acid and precipitated with a solution of 68 g. of silver nitrate in 200 cc. of water. The precipitated silver salt was filtered by suction and washed with water. It was suspended in water, acidified with acetic acid and treated with hydrogen sulfide at 60° with constant stirring for one and one-half hours. The silver sulfide was filtered off and washed. The combined filtrate and washings were partially decolorized with Norit A and evaporated to dryness *in vacuo* to yield 11 g. (39% yield) of 5-methylpyrazine-2,3-dicarboxylic acid, m. p. 163–164°. Recrystallized from an alcohol-ether mixture, the compound melted at 174–175°. It titrated as a strong acid and had a neutral equivalent of 93.0 (determined by potentiometric titration); calcd. 91.1. Aqueous solutions of this acid gave deep wine red colorations with ferrous sulfate.

Anal. Calcd. for $C_7H_6O_4N_2$: C, 46.15; H, 3.32; N, 15.36. Found: C, 46.40; H, 3.69; N, 14.33.

S-Benzylthiuronium salt prepared according to Donleavy[3]; m. p. 203–204°, after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{23}H_{26}O_4N_6S_2$: C, 53.65; H, 5.09; N, 16.34; S, 12.45. Found: C, 53.40; H, 5.09; N, 16.65; S, 12.10.

6-Methylpyrazine-2-carboxylic Acid.—One gram of 5-methylpyrazine-2,3-dicarboxylic acid was placed in a vacuum sublimation apparatus and was decarboxylated by heating to 175–185° at 1 mm. with simultaneous sublimation to yield 0.6 g. (82%) of 6-methylpyrazine-2-carboxylic acid, m. p. 135–140°. After two resublimations at 100–110° (1 mm.) the compound melted sharply at 138–140° (turbid melt which became clear at 144 with the evolution of a gas). Neutral equivalent by potentiometric titration was 136; calcd. 138. The ferrous sulfate color test gave orange coloration.

Anal. Calcd. for $C_6H_6O_2N_2$: C, 52.19; H, 4.38; N, 20.29. Found: C, 52.31; H, 4.21; N, 20.21.

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[1] Böttcher, *Ber.*, **46**, 3084 (1913).

[2] Stoehr, *J. prakt. Chem.*, [2] **47**, 480 (1893).

[3] Donleavy, THIS JOURNAL, **58**, 1004 (1936).

CHEMISTRY DEPARTMENT
POLYTECHNIC INSTITUTE OF BROOKLYN
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RECEIVED OCTOBER 5, 1945

Interaction Energies and Thermochemical Data

BY JOHN R. LACHER[1]

Recently Aston, *et al.*,[2] have been able to calculate empirically the height of potential barriers hindering internal rotation. They assumed that the barrier was due to a repulsion between hydrogen atoms. Urey and Bradley,[3] in discussing the normal vibrations of carbon tetrachloride and similar compounds, found it necessary to assume the existence of repulsive forces between the atoms situated at the corners of a tetrahedron. These latter forces were in addition to those directed along and perpendicular to the chemical bonds. H. A. Stuart,[4] V. Deitz,[5] R. Serber,[6] and E. Mack[7] have already indicated that interaction energy due to the repulsion (and in some situations certainly due to the attraction) of certain groups should be taken into account in the interpretation of thermochemical data. It is desired here to illustrate and develop this idea further in connection with groups arranged tetrahedrally

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[1] Present address: Department of Chemistry, University of Colorado, Boulder, Colorado.

[2] J. G. Aston, S. Isserow, G. J. Szasz and R. M. Kennedy, *J. Chem. Phys.*, **12**, 336 (1944).

[3] H. C. Urey and C. A. Bradley, Jr., *Phys. Rev.*, **38**, 1969 (1931).

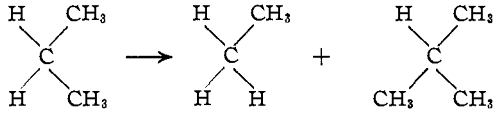
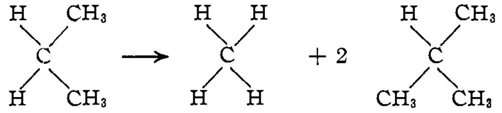
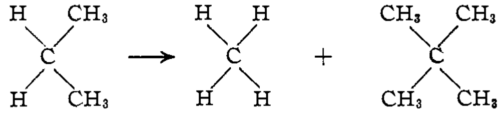
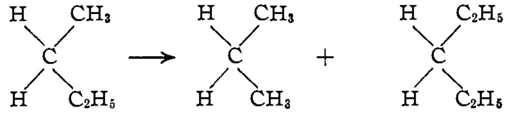
[4] H. A. Stuart, *ibid.*, **38**, 1372 (1938).

[5] V. Deitz, *J. Chem. Phys.*, **3**, 58, 436 (1935).

[6] R. Serber, *ibid.*, **3**, 81 (1935).

[7] E. Mack, Jr., *J. Phys. Chem.*, **41**, 221 (1937).

about a central carbon atom. Accordingly the heats of the following reactions were calculated from the data of Rossini.[8] In these reactions the number of carbon–carbon and carbon–hydrogen bonds remains unchanged. There has taken place merely a redistribution of hydrogen atoms, methyl, and ethyl groups about a central carbon atom. The heats of the first three reactions are in the ratio of one, three and four. This may be interpreted by assigning a repulsion to the hydrogen atoms and methyl groups arranged about the central carbon atom and by assuming that the repulsive forces are directed along the six edges of a tetrahedron. The net effect in reaction I is the conversion of two hydrogen–methyl interactions into a hydrogen–hydrogen and a methyl–methyl interaction. In reactions II and III the number of hydrogen–methyl conversions is simply three and four times as many as for I. This result may be summarized as

No.	Reaction*	*H*, cal.
I	2 	−2041
II	3 	−6315
III	2 	−7775
IV	2 	−59

$$2H\cdot CH_3 \longrightarrow H\cdot H + CH_3\cdot CH_3;\ \Delta H = -2030 \pm 100 \text{ cal.}$$

In reaction IV, the net effect is the conversion of two methyl–ethyl repulsions into one methyl–methyl and one ethyl–ethyl. Since the heat effect is zero, we may write

$$2CH_3\cdot C_2H_5 \longrightarrow CH_3\cdot CH_3 + C_2H_5\cdot C_2H_5 \qquad \Delta H \sim 0$$

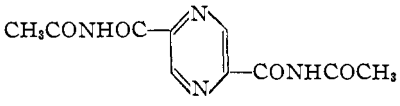
The composition of equilibrium mixtures of tetraethyl and tetramethyl lead is determined, according to Calingaert and Beatty,[9] merely by the external symmetry numbers of the molecules involved. Stearn[10] pointed out that this means that the heat of the redistribution reaction must be zero.

JACKSON LABORATORY
E. I. DU PONT DE NEMOURS AND COMPANY, INC.
WILMINGTON, DELAWARE
RECEIVED SEPTEMBER 21, 1945

Syntheses in the Pyrazine Series. Preparation of 2,5-Dicyanopyrazine and the Diacetyl Diamide of Pyrazine Dicarboxylic Acid-2,5

BY IRVING J. KREMS AND PAUL E. SPOERRI

Since Braun[1] and Tscherniac had reported that phthalic acid diamide undergoes a semi-dehydration to the amido nitrile when treated with acetic anhydride, we subjected the diamide of pyrazine dicarboxylic acid-2,5[2] to the same treatment. No change was detected after four hours; after forty-eight hours of refluxing, crystals of the diacetyl diamide (I) were obtained.



I

When a suspension of the diamide in nitrobenzene was treated with phosphorus pentoxide, the dinitrile was produced in low yield.

Experimental

Pyrazine Dicarboxylic Acid-2,5.[3]—Since the yields were quite poor the conditions of the permanganate oxidation of 2,5-dimethylpyrazine were modified. The results showed that the yield was independent of the permanganate concentration between two and twenty per cent., and the time of addition of the oxidizing solution between one and thirty-six hours, but was favored by an increase in *p*H. An oxidation of the insoluble mercuric chloride double salt instead of the free base indicated no protection to the pyrazine nucleus.

Twenty-seven grams of dimethylpyrazine[4,5] was dissolved together with 5 g. of potassium hydroxide in 150 ml. of water and warmed on the steam-bath in a 2,000 ml. three-necked round-bottom flask fitted with a separatory funnel, thermometer, condenser and stirrer. A hot solution of 158 g. of potassium permanganate in 760 ml. of water was added slowly over a period of one hour with stirring, the temperature being kept at 75°. Stirring was maintained for another half hour at the same temperature, after which the mixture was allowed to cool and stand overnight. The precipitate was filtered off and washed several times with hot water. The filtrate was evaporated to small volume, acidified with dilute nitric acid, and allowed to stand for one hour. The free diacid was filtered off, washed thoroughly with hot water, dissolved with hot dilute ammonium hydroxide and reprecipitated with dilute nitric acid. The precipitate was filtered off and dried *in vacuo* over sulfuric acid; yield 1.68 g., m. p. 253° (seal cap).

The Diacetyl Diamide of Pyrazine Dicarboxylic Acid 2,5 (I).—One-half gram of the diamide of pyrazine dicarboxylic acid-2,5[2] and 15 ml. acetic anhydride were placed in 50 ml. flask fitted with a two-foot length of glass tubing as an air condenser. Care was taken to eliminate moisture, and the air condenser was fitted with a calcium chloride tube. The mixture was refluxed for forty-eight hours at the end of which time it had turned completely black. It was allowed to cool, and then was placed in the ice chest for twenty-four hours. The resultant crystals were filtered

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[8] F. D. Rossini, *Chem. Rev.*, **27**, 1 (1940).

[9] Calingaert and Beatty, THIS JOURNAL, **61**, 2748 (1939).

[10] Stearn, *ibid.*, **62**, 1630 (1940).

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(1) Braun and Tscherniac, *Ber.*, **40**, 2710 (1907).

(2) Spoerri and Erickson, THIS JOURNAL, **60**, 400 (1938).

(3) Stoehr, *Ber.*, **24**, 4108 (1892).

(4) Étard, *Compt. rend.*, **92**, 460, 795 (1881).

(5) Stoehr, *J. prakt. Chem.*, [2] **43**, 156 (1891); **47**, 439 (1893).

off, washed with acetic anhydride until the filtrate was almost colorless and then recrystallized from glacial acetic acid. After another recrystallization from the same solvent with the aid of a small amount of nuchar small white prisms were obtained; yield 0.15 g., m. p. 270–272°.

Anal.[6] Calcd. for $C_{10}H_{10}O_4N_4$: C, 47.97; H, 4.02. Found: C, 47.56; H, 4.23.

2,5-Dicyanopyrazine.—Attempts to totally dehydrate the diamide of pyrazine dicarboxylic acid-2,5 by a twenty-hour reflux with thionyl chloride, heating with phosphorus pentoxide at 320° for seven hours, and a straightforward distillation with the latter reagent, brought about little but decomposition. The following procedure was successful.

Eight-tenths gram of the diamide of pyrazine dicarboxylic acid-2,5[2] together with 10 g. of phosphorus pentoxide and 35 ml. of freshly distilled nitrobenzene were placed in a 50-ml. flask fitted with an air condenser, precautions against moisture being taken. The mixture was refluxed for four hours. The residue was filtered off, and washed three times with hot nitrobenzene; the combined filtrates were evaporated down to 2 ml. and then chilled. The crystals thus obtained were filtered off and recrystallized from ethyl ether with the aid of a pinch of nuchar. The yield was 0.03 g., m. p. 188–189°; white glistening plates soluble in benzene, nitrobenzene and ethyl ether; insoluble in petroleum ether and water.

Anal.[7] Calcd. for $C_6H_2N_4$: C, 55.38; H, 1.55. Found: C, 55.57; H, 2.03.

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[6] Microanalysis by Wm. Saschek, N. Y.

[7] Microanalysis by Arlington Laboratories, Fairfax, Va.

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN 2, NEW YORK

RECEIVED OCTOBER 5, 1945

Polarographic Analysis of Streptomycin

BY GABOR B. LEVY, PHILIP SCHWED AND J. WARREN SACKETT

In the recovery and purification of streptomycin,[1] as in all similar work (for instance with penicillin), the availability of a rapid and precise method of analysis (assay) is of fundamental importance. Such a method has not been available. Therefore, the development of a chemical method of analysis has been investigated.

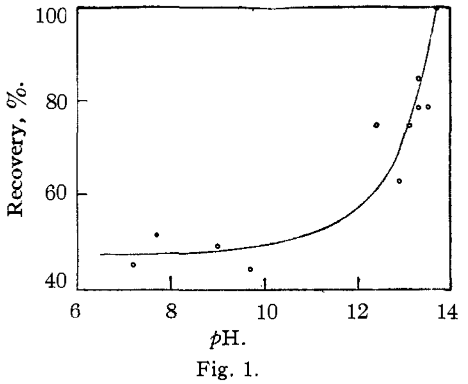

Fig. 1.

It was found that in alkaline medium, well-defined polarographic waves can be obtained with streptomycin solutions under certain conditions. By rigid standardization a method was obtained by which solutions of partially purified[2] streptomycin, which contain 200 μ/ml. or more, can be analyzed.

As a supporting electrolyte we used tetramethylammonium hydroxide (3% in the final solution) the use of which eliminates maxima and which maintains the *p*H at a sufficiently high level. This is important since the lowering of the *p*H causes a rapid diminishing of the diffusion current and concurrently appearance of irregularities. The level of *p*H 13.6 to 13.8 when resulting from tetramethylammonium hydroxide in 3% concentration does not act destructively on streptomycin at 13.6° within an hour. The influence of the *p*H on polarographic analysis is represented in Fig. 1 and it is evident that *p*H conditions should not be varied.

The effect of temperature on the diffusion current is 3%/°C. around room temperature which is comparable to the effect found in other polaro-

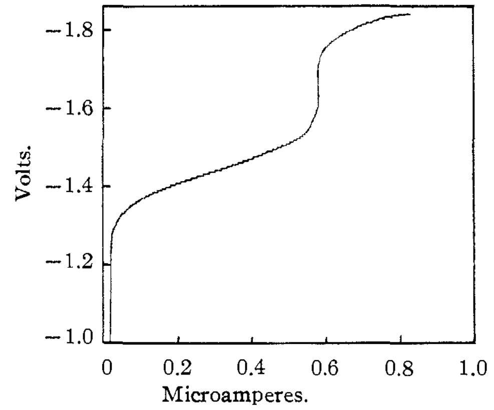

Fig. 2.

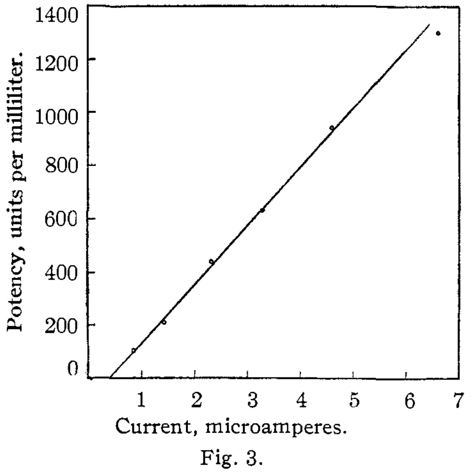

Fig. 3.

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[1] Carter, *et al.*, *J. Biol. Chem.*, **160**, 337 (1945); also Peck, *et al.*, THIS JOURNAL, **67**, 1866 (1945).

[2] Broth containing streptomycin and in some instances salt solutions contain materials which interfere with the analysis by producing additional polarographic waves. Preliminary work indicated that after precipitation of the impurities by lead ions and the removal of the excess lead by sulfuric acid, solutions were obtained which could be analyzed.

graphic analyses.[3] At elevated temperatures, *e. g.*, 40°, erratic results were obtained and the analysis could not be performed. The effect of solvents such as methanol and ethanol is marked and special calibration curves were made for solutions containing such solvents. The complete removal of dissolved oxygen is particularly important at lower levels of streptomycin concentration. Since sulfite interferes with the analysis, for this purpose nitrogen is bubbled through the sample.

In aqueous solutions at 13.6° in 3% tetramethylammonium hydroxide experimental points obtained in calibration (Fig. 2) over the range of 100–1000 μ/ml. fell on a straight line with an average deviation of only ±13 units. A typical polarogram is given in Fig. 3. It appeared from comparisons that in the electrochemical reaction one electron is involved, assuming reversibility. The half-wave potential is -1.45 v. measured against a mercury anode. This potential is subject to some shifting. The diffusion coefficient was found to be 3×10^{-6} cm.^{2} sec.$^{-1}$, which is of the order to be expected. Nevertheless, the possibility of a catalytic wave is not to be excluded.

When the results of the polarographic analyses are compared with the corresponding micro-biological assay results, very close agreement is found. This is true of solutions of low and high purity and in streptomycin produced in these laboratories as well as some originating from other sources. Twenty-five consecutive samples of streptomycin whose approximate purity varied from 70–800 μ/mg. were assayed both by the polarographic and the microbiological methods. The average deviation of the polarographic values from those obtained by the microbiological method was ±6%, which is well within the accuracy of the latter method. In only two instances were the deviations greater than 14.5%, namely, -31 and 25%, and these were in streptomycin received from outside sources.

It appears, therefore, that a more precise and considerably more rapid method for the analysis of streptomycin than available heretofore has been developed. Thus, although in two instances we found unexplained deviations, and although we are not certain of the nature of the electrochemical reaction on which the analysis is based, we feel justified in presenting this method at this time. In doing so we have two aims. First, we wish to make available to others working in the field a rapid method of analysis for streptomycin by which the time required for the analysis is reduced to fifteen minutes. Second, we hope that by the extensive use of the method by others, an answer may be found sooner to the few points mentioned above and more generally to some aspects of the streptomycin problem.

We wish to acknowledge gratefully the interest and advice of Dr. A. J. Liebmann and the cooperation of the microbiological assay department under G. A. Snyder.

SCHENLEY RESEARCH INSTITUTE, INC.
LAWRENCEBURG, INDIANA RECEIVED NOVEMBER 23, 1945

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[3] *E. g.* Kolthoff and Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

The Use of Calcium Carbide in the Synthesis of Isopropylidene Glycerol

BY M. MARTIN MAGLIO AND CHARLES A. BURGER

Fischer's[1] method for the synthesis of isopropylidene glycerol has recently been modified by Newman and Renoll,[2] so that the compound may be prepared quite easily in almost quantitative yield. There are several objections to the latter procedure, however, in that an extremely lengthy reaction time and special apparatus are required.

The present authors have succeeded in developing a method which eliminates these objections, although resulting in slightly smaller yields. The procedure consists chiefly in the inter-reaction of acetone and glycerol at reflux temperatures in the presence of an inert diluent, a surface active agent and a desiccant, calcium carbide. Of particular interest is the fact that in our method no acidic catalyst is employed. The surface active agent used, Advawet 15,[3] is the sodium salt of a sulfonated petroleum hydrocarbon mixture and is essentially neutral.

The physical properties of our twice-distilled product compare very favorably with those for Fischer's thrice-distilled.

Procedure.—A charge consisting of 110 g. of 95% glycerol, 200 ml. of solvent naphtha no. 4, 240 g. of acetone, 0.4 g. of Advawet 15 and 42 g. of calcium carbide was placed in a 1-liter, three-necked, round-bottomed electrically heated flask furnished wth a thermometer in one side neck, a reflux condenser in the other side neck and a mercury-sealed mechanical agitator in the center neck. The charge comprised one solid and two liquid phases. The charge was maintained at 58° and was agitated and refluxed for one hour when an additional 42 g. of desiccant was added (calcium carbide). The mixture was refluxed for an additional three hours, the liquid layer being homogeneous after this time. The cooled reaction mixture was neutralized with 1.5 g. of powdered, freshly fused sodium acetate and then 3 g. of sodium carbonate. After gravity filtration, the filtrate was fractionally distilled at atmospheric pressure, employing a ten-inch Vigreux column, to remove the solvent and the excess, unreacted acetone. Subsequently, distillation at reduced pressure resulted in an 84% yield (126 g.) of colorless isopropylidene glycerol, b. p. 79–81° (11 mm.), $n^{25}{}_D$ 1.4325, $d^{25}{}_4$ 1.0624. The odor of the finished product is foul, but it may be eliminated completely by means of activated carbon or some similar absorbent.

A longer reaction time increases the yield by as much as 5%. If the Advawet 15 is not used, the reaction time is somewhat longer and the yield is reduced to 80%.

RESEARCH LABORATORIES
ADVANCE SOLVENTS AND CHEMICAL CORPORATION
NEW YORK, N. Y. RECEIVED NOVEMBER 15, 1945

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[1] E. Fischer and Pfähler, *Ber.*, **53**, 1606 (1920).

[2] M. S. Newman and M. Renoll, THIS JOURNAL, **67**, 1621 (1945).

[3] Advawet 15 is a surface active agent sold by the Advance Solvents and Chemical Corporation.

The Heat of Formation of Boric Oxide

By B. J. Todd* and R. R. Miller

Bichowsky and Rossini[1] give for the heat of formation of boric oxide(gls) 279.9 kcal. per mole at 18° obtained from measurement of the heat of formation of boron trichloride(g) by Troost and Hautefeuille,[2] corrected according to Berthelot,[3] and from Berthelot's measurement of the heat of hydrolysis of boron trichloride(g).[3] Roth and Borger[4] give for the heat of formation of boric oxide(gls) 349 ± 3 kcal. per mole at 18° from data obtained by burning boron(s) in compressed oxygen, utilizing the heat of combustion of a known amount of paraffin oil to start the boron oxidation. We find the heat of formation of boric oxide under standard conditions to be 335.8 ± 0.8 kcal. per mole at 25°.

In this study, use was made of a Parr isothermal bomb calorimeter. The volume of the bomb empty was 350 ml. The water jacket surrounding the calorimeter was kept at 25.00 ± 0.01°. The temperature rise of the calorimeter was measured by means of a Beckmann thermometer calibrated at the Bureau of Standards. The heat transfer between jacket and calorimeter was calculated by Dickinson's[5] method, and the general procedure used for a calorimetric experiment was that specified in the A. S. T. M. Standard D-271-43 for coal. The calorimeter was calibrated by use of benzoic acid, standard sample No. 39f, according to the conditions described on its certificate from the Bureau of Standards. Six calibration experiments gave for the energy equivalent of the calorimeter 2413.0 ± 2.7 cal. per degree at a mean temperature of 25°, defining one calorie equal to 4.1833 international joules. Twelve blank calorimetric expts. gave for the energy correction used in firing the charge 22.0 ± 2.7 cal.

The spectroscopically pure boron used was prepared under the direction of Dr. H. I. Schlesinger at the University of Chicago by the thermal decomposition of diborane. A mixture of boron (approx. 0.1 g.) and benzoic acid (approx. 0.75 g.) was pelleted and burned in pure oxygen at an initial pressure of 40 atm. at 25°. A nickel–chromium crucible was used in Run I; a quartz crucible, in Run II. The weight of benzoic acid converted to carbon dioxide and to carbon was calculated from the initial weight of benzoic acid in the pellet and the weight of carbon dioxide formed in the combustion as determined by absorption with ascarite. The weight of boron oxidized was determined by titration with 0.1 *N* sodium hydroxide in the presence of mannitol under carbon dioxide-free conditions.

Calculation of ΔE for the reaction $2B(s) + 3/2O_2(g, 40\text{ atm.}) = B_2O_3(gls)$ at 25° was based on the bomb reaction represented by the equations

(a) $C_6H_5COOH(s) + 15/2O_2(g, 40\text{ atm.}) = 7CO_2(g) + 0.00045H_2O(g) + 2.99955H_2O(l)$ $\Delta E_a = -772.2$ kcal.

(b) $C_6H_5COOH(s) + 1/2O_2(g, 40\text{ atm.}) = 7C(s) + 3H_2O(l)$ $\Delta E_b = -118.0$ kcal.

(c) $2B(s) + 3/2O_2(g, 40\text{ atm.}) = B_2O_3(gls)$

(d) $B_2O_3(gls) + (3 + x)H_2O(l) = 2H_3BO_3$(satd. soln.) At 18°, according to Roth and Borger,[4] $\Delta E_d = -10.8$ kcal., if the boric oxide has been in contact with water for 15 min. This appears to be the least precise part of the calculations.

(e) Heat of ignition (electrical energy + combustion of 0.011 g. No. 38 B. and S. gage iron wire) equals 22 cal.

(f) Nitric acid formation was found to be negligible when the bomb was adequately flushed out with oxygen prior to filling.

The experimental results follow, where q_x refers to the heat evolved in reaction (x).

	Run I	Run II
G. $C_6H_5COOH \rightarrow CO_2 + H_2O$	0.7804	0.7394
G. $C_6H_5COOH \rightarrow C + H_2O$	.0000	.0050
G. B reacted	$.0413_2$	$.0494_4$
G. B_2O_3 formed	$.133_0$	$.159_1$
Total kcal. evolved	5.617	5.489
q_a	4.934	4.675
q_b	0.000	0.005
q_d	.020	.024
q_e	.022	.022
q_c	.641	.763
ΔE_c	$-335._6$	$-334._0$

Mean $\Delta E_c = -334._8$

For the reaction

(g) $3/2O_2(g, 25°, 40\text{ atm.}) = 3/2O_2(g. 25°$, unit fugacity) $\Delta E_g = 0.09$ kcal.[6] Combining (c) and (g) gives

(h) $2B(s) + 3/2O_2(g, 25°$, unit fugacity) $= B_2O_3(gls)$ $\Delta E_h = -334._9$ kcal.

To change to ΔH for this reaction, use is made of

$$\Delta H = \Delta E + RT\Delta n$$

Then for (h), $\Delta H = -335._8 \pm 0.8$ kcal.

The correction to convert ΔH_h at 25° to ΔH_h at 18° is negligible compared with the experimental error.

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* Present address: Corning Glass Works, Corning, N. Y.

(1) Bichowsky and Rossini, "The Thermochemistry of the Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936.

(2) Troost and Hautefeuille, *Ann. chim. phys.*, [5] **9**, 70–77 (1876); *Compt. rend.*, **70**, 252–255 (1870).

(3) Berthelot, *Ann. chim. phys.*, [5] **15**, 185–220 (1878); "Thermochimie," Gauthier-Villars, Paris, 1897.

(4) Roth and Borger, *Ber.*, **70B**, 48–54 (1937).

(5) Dickinson, *Bull. of Bur. of Standards*, **11**, 189 (1915).

(6) Rossini and Frandsen, *J. Research Natl. Bur. Standards*, **9**, 733 (1932).

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Effect of Hydrocarbon Bacteria on Racemic Mixtures of Hydrocarbons

By John Turkevich and Lejaren Arthur Hiller, Jr.

In a previous communication[1] was described the isolation and study of a *Bacterium aliphaticum*. This organism will metabolize in simple inorganic media numerous aliphatic hydrocarbons from pentane to paraffin oil. The washed cells will also oxidize glucose and other sugars, as well as the hydrocarbons, through a cyanide-sensitive respiratory system. There is no evidence of an anaerobic metabolism. It is the purpose of this investigation to determine whether *Bacterium*

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(1) F. H. Johnson, W. T. Goodale and J. Turkevich, *J. Cellular Comp. Physiol.*, **19**, 163–172 (1942).

aliphaticum will preferentially attack the *d* or *l* form of a racemic hydrocarbon mixture.

Materials and Methods

The original pure culture of *Bacterium aliphaticum* was isolated with the aid of petroleum ether enrichment from the soil obtained at the base of a gasolene pump on a farm. The culture used in this investigation was obtained from a stock culture maintained on Söhngen's inorganic medium (0.05% ammonium chloride, 0.05% potassium hydrogen phosphate, a trace of calcium chloride) and on 5% petroleum ether (maximum boiling point 120°).

One of the hydrocarbons used was 3-methylheptane obtained from the American Petroleum Institute Ohio State University Manifest P-61 and was characterized by $n^{20}\text{D}$ 1.3998. The other hydrocarbon, 3-methylhexane, was obtained through the courtesy of Dr. J. O. Smith of the Research Laboratory of the Tidewater Associates Company. It was characterized by $n^{20}\text{D}$ 1.3884. Both of these hydrocarbons showed no rotation.

The optical activity was determined on a Franz Schmidt Research Polarimeter whose accuracy was +0.01°. A two-decimeter semi-micro polarimeter tube was used.

Two hundred milliliters of the nutrient solution and ten milliliters of the substrate hydrocarbon were placed in an 8-oz. prescription bottle and the thickness of the hydrocarbon layer was measured to a thirty-second of an inch. This mixture was then inoculated by means of a platinum loop with a stock culture growing on petroleum ether. All standard precautions were observed to prevent contamination. The prescription bottles were closed with screw caps and allowed to stand at room temperatures. Two or three days after inoculation a cloudiness appeared and this became more and more dense with time indicating ready metabolism of the hydrocarbons. A blank showed no growth. After three weeks the level of the hydrocarbon dropped to half its original value and the cultures were treated as follows: The hydrocarbon layer was separated from the aqueous layer by means of a separatory funnel and dried over anhydrous calcium chloride. The optical activity was found to be zero in the case of either of the two hydrocarbons. Another portion of the hydrocarbon layer was washed six times with concentrated sulfuric acid and subsequently six times with saturated magnesium sulfate solution. It was then twice washed with distilled water and dried over anhydrous magnesium sulfate. The optical activity was again found to be zero in both cases. The aqueous layer was centrifuged to precipitate the bacterial suspension, and the supernatant liquid was measured in the polarimeter. The optical activity was again zero in both cases. After these measurements the hydrocarbons were again used as substrate for the growth of *bacterium aliphaticum*. After three weeks the same procedure as above was used on the residual hydrocarbon which represented one-third of the volume of the original sample. The optical activity in both cases, that of 3-methylhexane and 3-methylheptane, was again zero.

Discussion.—It has been abundantly established since Pasteur's discovery that certain organisms especially molds, yeasts and bacteria metabolize preferentially one of the two optical antipodes of a racemic mixture.[2]

The results of the present investigation show that the *bacterium aliphaticum* does not attack preferentially one of the two optical isomers of 3-methylhexane and of 3-methylheptane. P. A. Levene and R. E. Marker[3] report an observed rotation of $[\alpha]_\text{D}$ +1.64° and a maximum rotation of $[\alpha]_\text{D}$ 9.67° for 3-methylhexane while we observe less than 0.01°. It, therefore, follows that if there is a preferential action in the rate of attack of the *bacterium aliphaticum* it is less than one part in two thousand. This result is not surprising in view of the variety of substrates that this organism can metabolize, *e. g.*, aliphatic hydrocarbons and sugars. It is further consistent with the results of F. H. Johnson and H. W. Schwarz[4] who found that this bacterium metabolized both *d* and *l* arabinose though no attempt was made to determine whether the rate of metabolism was the same.

It is, however, unfortunate that there is no preferential action on optical antipodes, for if there were, it would offer a method of obtaining a wide variety of optically active hydrocarbons for the study of the mechanism of hydrocarbon reactions.

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(2) *Cf.* H. Scheibler in J. Houben's "Die Methoden der organischen Chemie," Vol. 2, Part 2, Leipzig, 1925, p. 1087; R. L. Shriner, R. Adams and C. S. Marvel in Gilman's "Organic Chemistry," 1, 263 (1943).

(3) Levene and Marker, *J. Biol. Chem.*, **95**, 13 (1932).

(4) F. H. Johnson and H. W. Schwarz, *J. Bact.*, **47**, 373 (1944).

FRICK CHEMICAL LABORATORY
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Addition of Secondary Amines to Dibromopropanol

BY FRANK C. WHITMORE, HARRY S. MOSHER, DAVID P. SPALDING, ROBERT B. TAYLOR, GEORGE W. MOERSCH AND WILLIAM H. YANKO

We reported[1] that 2,3-dibromopropanol (I) reacts with secondary amines such as piperidine, diethylamine or morpholine to give the metathetical product (II).

$$\underset{\text{(I)}}{\text{HOCH}_2\text{CHBrCH}_2\text{Br}} + \text{HNR}_2 \longrightarrow \underset{\text{(II)}}{\text{HOCH}_2\text{CH(NR}_2\text{)CH}_2\text{NR}_2}$$

On the suggestion of Dr. P. H. Williams, of the Shell Development Company, Emeryville, California, we have re-investigated these products, and have found in at least one case, *i. e.*, piperidine, that the symmetrical compound

$$\text{R}_2\text{NCH}_2\text{CHOHCH}_2\text{NR}_2 \quad \text{(III)}$$

is formed as well.

Thus, when piperidine was treated with 2,3-dibromopropanol and the product distilled from a Claisen flask, the first portion of the amine fraction gave a picrate, m. p. 190–191°, which showed no depression of the melting point when mixed with the picrate from the reaction product of piperidine and epichlorohydrin. This must be the symmetrical 1,3-dipiperidino-2-hydroxypropane (III). The last fraction from the distillation gave a picrate melting at 174–175° and showed the same melting point when mixed with the picrate from the product of the Bouveault–Blanc reduction of ethyl 2,3-dipiperidionpropionate. This must be the picrate of the metathetical reaction product, 2,3-dipiperidino-

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(1) Whitmore, *et al.*, THIS JOURNAL, **67**, 664 (1945).

1-hydroxypropane (II) reported in the above reference.

The formation of the symmetrical isomer probably arises from the intermediate ethylene oxide.

DEPARTMENT OF CHEMISTRY
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THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA
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The Uronic Acid Component of Heparin

BY M. L. WOLFROM AND F. A. H. RICE

Sulfuric acid and D-glucosamine[1] have been the only identified hydrolytic products of heparin, the blood anticoagulant isolable from animal tissues. Qualitative[2] and quantitative data[3] indicating the presence of a uronic acid in heparin have been obtained. It has been demonstrated[4] that the hydrolytic conditions which will liberate the uronic acid can also readily destroy it since it is decomposed by acidity. We have accordingly subjected crystalline barium acid heparinate to oxidative hydrolysis, considering that any uronic acid liberated might be stabilized as the acid-resistant dibasic acid. From the reaction mixture there was isolated D-glucosaccharic acid (as the crystalline potassium acid salt) and crystalline D-glucosaminic acid. Under similar non-oxidative hydrolytic conditions, no D-glucosaccharic acid was isolable. These results therefore establish the uronic acid component of heparin as D-glucuronic acid. We wish to remark that the optical rotation of our isolated D-glucosaccharic acid was ascertained, a significant point generally overlooked in most isolations of this substance.

Experimental

An amount of 200 mg. of crystalline barium acid heparinate was dissolved in 2 cc. of water and cooled to near 0°. Five drops of bromine were added, followed by the gradual addition, over a period of ten minutes, of a total of 5 cc. of concentrated sulfuric acid. The mixture was allowed to stand at *ca.* 3° for one week. From time to time, as the solution became less colored, a few drops more of bromine were added. The solution was finally kept at room temperature for *ca.* five hours, aerated to effect bromine removal, and poured into 75 cc. of cold (near 0°) water. The sulfuric acid was neutralized in the cold with barium carbonate and the mixture filtered. Concentration (30–40°) of the filtrate under reduced pressure yielded a thick sirup.

The sirup was acidified with a drop of concentrated hydrochloric acid and extracted at room temperature with 95% ethanol. The extract was neutralized to *ca.* *p*H 6 with 10% aqueous potassium hydroxide, filtered and concentrated under reduced pressure to a thick sirup. The sirup was treated with 10 cc. of absolute ethanol, filtered and again concentrated under reduced pressure to a sirup. This sirup was dissolved in 1 cc. of water, neutralized with solid potassium carbonate and 1 cc. of glacial acetic acid added. Crystals formed overnight that had the appearance of potassium acid saccharate when viewed under the microscope. A further quantity of like crystals were obtained by extracting the barium sulfate (formed above in the neutralization of the sulfuric acid) at room temperature with 10 cc. of 1% aqueous potassium hydroxide. The neutralized (with acetic acid) extract was concentrated (30–40°) under reduced pressure to a volume of 1 cc. and acidified with an equal volume of glacial acetic acid. Crystals formed on standing overnight; total yield 29.9 mg., $[\alpha]^{20}_D$ +10° (*c* 2.5 as dipotassium salt, water). The polarization was effected by solution in an equivalent (to phenolphthalein) amount of aqueous potassium carbonate solution. A known sample of potassium acid D-glucosaccharate gave the same value, $[\alpha]^{20}_D$ +10°, under the same conditions. The solutions were colored slightly yellow by the neutralization procedure.

Anal. Calcd. for $C_6H_9O_8K$: K, 15.72. Found: K, 15.82.

The crystalline product was therefore identified as potassium acid D-glucosaccharate.

The insoluble material remaining after the ethanol extraction described above was treated with a small amount of silver carbonate and extracted at room temperature with 25 cc. of 95% ethanol. The extract was concentrated to 5 cc., filtered and ether added to incipient opalescence. Crystals (long needles) separated on standing; yield 26 mg., dec. 250–260°, $[\alpha]^{21}_D$ −19 ± 2° (*c* (as weighed) 1.0, 2.5% hydrochloric acid, twelve hours). The crystals were acid toward litmus and contained amino nitrogen (by soda-lime fusion). A crystalline copper salt (bluish-green crystals) was formed with cupric carbonate. These data identify the substance as D-glucosaminic acid,[5] for which Fischer and Leuchs[6] cite the constants: dec. 250°, $[\alpha]^{18}_D$ $-17° \rightarrow -15°$ (*c* 10, 2.5% hydrochloric acid, thirty hours).

On repeating the above described hydrolysis of crystalline barium acid heparinate but omitting the bromine, no potassium acid D-glucosaccharate was formed.

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[1] E. Jorpes and S. Bergström, *Z. physiol. Chem.*, **244**, 253 (1936).

[2] W. H. Howell, *Bull. Johns Hopkins Hosp.*, **42**, 199 (1928).

[3] M. L. Wolfrom, D. I. Weisblat, J. V. Karabinos, W. H. McNeely and J. McLean, THIS JOURNAL, **65**, 2077 (1943).

[4] M. L. Wolfrom and J. V. Karabinos, *ibid.*, **67**, 679 (1945).

[5] E. Fischer and F. Tiemann, *Ber.*, **27**, 138 (1894).

[6] E. Fischer and H. Leuchs, *ibid.*, **35**, 3787 (1902); **36**, 24 (1903).

CHEMICAL LABORATORY
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO
RECEIVED DECEMBER 17, 1945

NEW COMPOUNDS

3-Trichloromethyl-6-hydroxy-7-chlorophthalide and its Acetyl Derivative

The hydroxyphthalide was prepared by Chattaway and Calvet's method.[1] Three grams of 2-chloro-3-hydoxybenzoic acid and 4 g. of U. S. P. chloral hydrate were dissolved in 30 g. of concentrated sulfuric acid. After standing twenty-four hours, the solution was poured into cracked ice and water, and the precipitate, which formed, when washed with water and dried weighed 5.2 g. and melted at 190–192°. One crystallization from benzene and two from ethanol–water raised the melting point to 195.5–196°. The compound forms a precipitate when warmed with alcoholic silver nitrate, is readily soluble in 5% aqueous sodium hydroxide solution, and produces a green fluorescence with resorcinol and sulfuric acid.

Anal. Calcd. for $C_9H_4Cl_4O_3$: Cl, 46.97. Found: Cl, 46.91, 46.94.

The acetyl derivative was prepared by the method of Pratt and Robinson.[2] Five-tenths gram of the hydroxyphthalide gave 0.48 g. of a product melting at 175–177°.

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[1] Chattaway and Calvet, *J. Chem. Soc.*, 1092 (1928).

[2] Pratt and Robinson, *ibid.*, **127**, 1184 (1925).