NOTES

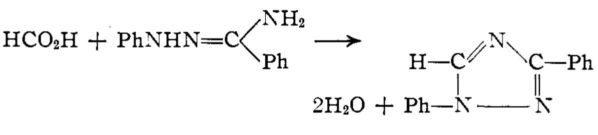
Synthesis of 1,3-Diphenyl-1,2,4-triazole

By M. R. Atkinson[1] and J. B. Polya

Received August 12, 1952

Einhorn, Bischkopff and Szelinski[2] reported the preparation of 1,3-diphenyl-1,2,4-triazole (I) from phenylhydrazine and N-formylbenzamide in 30% aqueous acetic acid. Thompson[3] showed that this reaction affords 1,5-diphenyl-1,2,4-triazole (II) identical with the preparations of Young[4] and Cleve.[5] We were able to confirm the work of Thompson and showed that II is obtained, although in inferior yield, when pyridine containing pyridinium hydrochloride is used instead of dilute acetic acid.[6]

It was necessary to synthesize I in order to assess the work of Einhorn and his collaborators as the physical data characterizing their triazole differ from those which apply to II by the agreement of other authors. The synthesis of I was accomplished by the method of Ponzio[7] which has been found useful in other triazole syntheses.[6,8] Benzamide phenylhydrazone heated with formic acid affords I in a yield of 36%. I, its hydrochloride and picrate differ from the corresponding products described by Einhorn and collaborators.



Experimental

Benzamide phenylhydrazone was prepared by the method of Voswinkel[9] and purified through its picrate, m.p. 196–198°. Benzamide phenylhydrazone (7.20 g.) was refluxed with 99% formic acid (8.0 ml.) on the water-bath for 90 minutes. The product was adjusted to *p*H 8 with aqueous 10% sodium carbonate and extracted with ether (3 × 50 ml.). Distillation of the dried ether extract between 160–220° (2 mm.) afforded oily crystals (4.5 g.) which were dissolved in dry ether (150 ml.) and treated with dry hydrogen chloride to precipitate the hydrochloride of I as a white, microcrystalline powder, m.p. 192–194° (Einhorn, *et al.*, 176°) in a yield of 5.73 g. *Anal.* Calcd. for $C_{14}H_{11}N_3 \cdot HCl$: Cl, 13.76. Found: Cl, 13.70.

The hydrochloride was decomposed with aqueous 10% sodium carbonate (100 ml.) and extracted with ether (3 × 50 ml.) to afford on removing the solvent colorless prismatic crystals of I, m.p. 79–81° (2.71 g., 36%). Purification through the picrate, yellow needles from ethanol, m.p. 161–161.5° (*Anal.* Calcd. for $C_{14}H_{11}N_3.C_6H_3O_7N_3$: C, 53.33; H, 3.11; N, 18.67. Found: C, 53.35; H, 3.24; N, 17.67) (Einhorn, *et al.*, 148°) and two recrystallizations from petroleum ether (60–80°) raised the m.p. to 82.5–83° (Einhorn, *et al.*, 96–97°).

Anal.[10] Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.34; H, 5.33; N, 19.18.

The triazole and its picrate depress the m.p.'s of authentic II and its picrate,[3] respectively.

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[1] Imperial Chemical Industries of Australia and New Zealand Research Fellow.

[2] A. Einhorn, E. Bischkopff and B. Szelinski, *Ann.*, **343**, 227 (1905).

[3] Q. E. Thompson, This Journal, **73**, 5914 (1951).

[4] G. Young, *J. Chem. Soc.*, **67**, 1069 (1895).

[5] A. Cleve, *Ber.*, **29**, 2679 (1896).

[6] M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, in press, (1952).

[7] G. Ponzio, *Gazz. chim. ital.*, **40** I, 85 (1910).

[8] D. Jerchel and R. Kuhn, *Ann.*, **568**, 185 (1950).

[9] H. Voswinkel, *Ber.*, **36**, 2484 (1903).

[10] Microanalyses by Dr. W. Zimmermann, Commonwealth Scientific and Industrial Research Organization, Melbourne.

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The High Field Conductance of an Aqueous Solution of Cadmium Chloride at 25°[1]

By Frederick Eugene Bailey, Jr., and Andrew Patterson, Jr.

Received November 7, 1952

The unusual behavior of cadmium halides in aqueous solution has been the basis for much discussion in the past.[2] Harned and Fitzgerald found that the behavior of aqueous solutions of cadmium chloride in electrolytic cells might be adequately explained[3] in terms of an equilibrium

$$CdCl^+ \rightleftarrows Cd^{++} + Cl^-;\ K(0) = 0.011 \text{ at } 25° \quad (1)$$

it being assumed that the dissociation of $CdCl_2$ into $CdCl^+$ and Cl^- is complete. To investigate this electrolyte from another point of view, we have determined the high field conductance of an aqueous solution of cadmium chloride, 1.697×10^{-4} molar, at 25° relative to potassium chloride.

The procedure employed was identical with that of Gledhill and Patterson.[4] Baker and Adamson C.P. cadmium chloride was recrystallized once from conductivity water; the resulting hydrate was dried for four days in a vacuum oven at 70°, ground in an agate mortar, and again dried for four days in a vacuum oven at 70°. The resulting salt, assumed to be anhydrous, was then stored for use. Both the cadmium chloride and reference electrolyte, potassium chloride, were prepared by weighing in the form of strong stock solutions and then weight diluted to the desired concentrations in the conductance cells. The concentrations were: cadmium chloride, 1.697×10^{-4} molar; potassium chloride, 2.889×10^{-4} molar. The temperature was 25 ± 0.015°.

The results are shown in Fig. 1 for two determinations on the same solution. At 200 kv./cm. the fractional high field conductance quotient, $\Delta\lambda/\lambda_0$, has the value 1.07%; this value may be compared with those for potassium chloride, approximately 0.4%, and magnesium sulfate, approximately 3.3%, at the same field. No theory is currently available to permit computation of values for non-symmetrical valence-type electrolytes, although as a rough

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[1] Contribution No. 1133 from the Department of Chemistry, Yale University.

[2] N. V. Sidgwick, "The Chemical Elements and Their Compounds," Oxford University Press, New York, N. Y., 1950, p. 274.

[3] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd ed., Reinhold Publ. Corp., New York, N. Y., 1950 pp. 418–421.

[4] J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, **56**, 999 (1952).

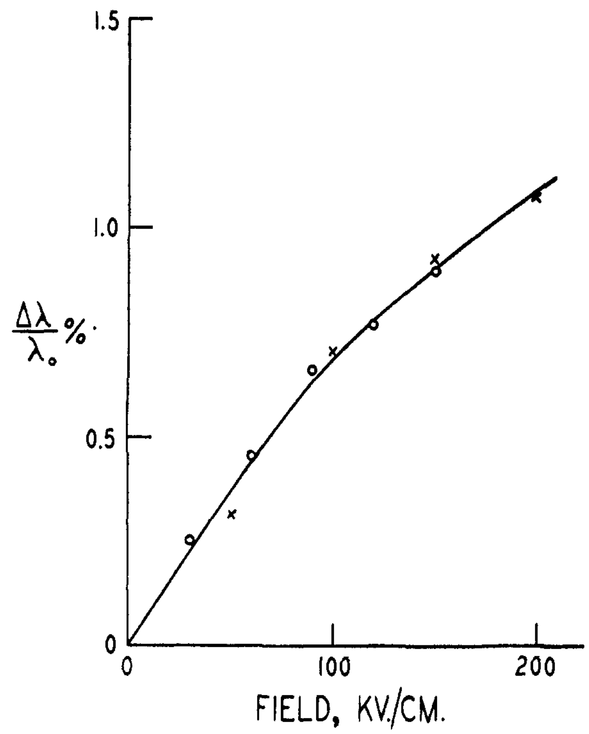

Fig. 1.—The high field conductance of an aqueous solution of cadmium chloride, 1.697 × 10^{-4} molar, relative to potassium chloride at 25°.

approximation the increase in equivalent conductance has been found[3] to be proportional to $(z_+z_-)^2$; thus, $(z_+z_-)^2 = 4$, and 4 × 0.4 (for potassium chloride) = 1.6%. The curve has a shape something like that of a strong electrolyte, but fails to bend over at so low a field or in so pronounced a manner as does magnesium sulfate, for example.

Determinations on similar valence-type, but stronger, electrolytes, *e.g.*, calcium chloride, are now under way. When completed, these will offer more information on the influence on the high field behavior of the weak ionization referred to in equation 1, above.

Acknowledgment.—This work was supported by the Office of Naval Research.

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Quaternary Salts of Halogenated Heterocyclic Nitrogen Compounds[1]

BY CARL TABB BAHNER, WILLIAM K. EASLEY, GEORGE E. BIGGERSTAFF, EMMA BROWN, MARGUERITE CLOSE, MARY MARGUERITE ISENBERG, HAROLD D. LYONS, LILBURN NORTON, EMOGENE STEPHEN, BILLY STUMP, BETTY GAY WALDEN BLANC AND MARY WATKINS

RECEIVED NOVEMBER 22, 1952

A previous article[2] has reported the preparation of quaternary salts of halogenated pyridines and quinolines for screening against tumors in mice. The series have been extended by synthesis of the salts of 2-chloropyridine and 3-bromopyridine listed in Table I and the salts of 3-bromoquinoline, 6-chloroquinoline and 4,7-dichloroquinoline listed in Table II. Results of screening tests at the National Cancer Institute are to be published elsewhere.

4,7-Dichloroquinoline was particularly unreactive and was recovered unchanged from mixtures with several halogen compounds although a small quantity of quaternary salt was obtained in a few cases. Attempts to prepare quaternary salts of 8-chloroquinoline by reaction of the base with substituted phenacyl bromides at 45° produced the hydrobromide as the chief crystalline product instead of the expected quaternary salt.

TABLE I

SALTS OF SUBSTITUTED PYRIDINES

Salt from 2-Chloropyridine and:	Empirical formula	M.p., °C.	Ionic halogen, % Calcd.	Ionic halogen, % Found[a]
p-Methoxyphenacyl bromide	$C_{14}H_{13}BrClNO_2$	171	23.32	23.04
β-Naphthacyl bromide	$C_{17}H_{13}BrClNO$	175	22.04	22.00
5,6,7,8-Tetrahydro-β-naphthacyl bromide	$C_{17}H_{17}BrClNO$	190	21.79	21.69
4,4'-Bis-(bromoacetyl)-phenyl ether	$C_{26}H_{20}Br_2Cl_2N_2O_3$	210	25.01	24.79
3-Bromopyridine and:				
β-Phenylethyl iodide	$C_{13}H_{14}BrIN$	152–154	32.45	32.29
Iodoacetone	C_8H_9BrINO	180	37.10	37.29
Glycerol-α-monochlorohydrin	$C_8H_{11}BrClNO_2$	216	13.20	13.07
Iodoacetonitrile	C_7H_6BrIN	177–178	39.06	38.83
4,4'-Bis-(bromoacetyl)-phenyl ether	$C_{26}H_{20}Br_4N_2O_3$	220	21.95	21.52

[a] Average of two analyses.

TABLE II

QUATERNARY SALTS OF HALOGENATED QUINOLINES

Salt from	Empirical formula	M.p., °C.	Ionic halogen, % Calcd.	Ionic halogen, % Found[a]
3-Bromoquinoline and:				
Glycerol-α,γ-dibromohydrin	$C_{12}H_{12}Br_3NO$	251	18.76	18.91
3,4-Dihydroxyphenacyl chloride	$C_{17}H_{13}BrClNO_3$	245	[b]	
p-Methoxyphenacyl bromide	$C_{18}H_{15}Br_2NO_2$	241	18.28	18.30
p-Chlorophenacyl bromide	$C_{17}H_{12}Br_2ClNO_2$	240	18.10	18.15
p-Bromophenacyl bromide	$C_{17}H_{12}Br_3NO$	237	16.45	16.63
6-Bromoquinoline and:				
Glycerol-α,γ-dibromohydrin	$C_{12}H_{12}Br_3NO$	241	18.76	19.05
Allyl bromide	$C_{12}H_{11}Br_2N$	171	24.29	24.07
6-Chloroquinoline and:				
Iodoacetone	$C_{12}H_{11}ClINO$	186–187	36.50	36.54
p-Iodophenacyl bromide	$C_{17}H_{20}BrClINO$	230	16.36	16.32
4,7-Dichloroquinoline and:				
Phenacyl bromide	$C_{15}H_{12}BrCl_2NO$	163	20.12	19.93
p-*t*-Butylphenacyl bromide	$C_{12}H_{20}BrCl_2NO$	185–186	17.68	17.50

[a] Average of two analyses. [b] Calcd.: C, 51.73: H, 3.32. Found: C, 51.58; H, 3.49.

8-Chloroquinoline Hydrobromide.—Prepared by direct reaction of equimolecular quantities of the base and concentrated hydrobromic acid or as the principal crystalline prod-

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[1] This research was supported in part by a research grant from the National Institutes of Health, U. S. Public Health Service, and in part by a grant from the Damon Runyon Memorial Fund for Cancer Research.

[2] C. T. Bahner, W. K. Easley, M. D. Pickens, H. D. Lyons, L. L. Norton, B. G. Walden and G. E. Biggerstaff, THIS JOURNAL, **73**, 3499 (1951).

uct of the reaction of *p*-methoxyphenacyl bromide with 8-chloroquinoline and recrystallized, this is a white, water-soluble salt, m.p. 222–223° (dec.).

Anal. Calcd. for C_9H_9BrCl: Br, 32.94. Found: Br, 32.89, 32.99.

Since quaternary salts of 2-halopyridines have been shown to have a reactive halogen atom and to be converted into N-substituted 2-pyridones in alkaline solution,[3] it seems likely that this change occurs in the blood stream of animals after the compound has been injected. A pyridone was prepared for comparison of its effect with those of the parent compound.

1-*p*-Fluorophenacyl-2-pyridone.—Two grams of 1-*p*-fluorophenacyl-2-chloropyridinium bromide and 1.64 g. of Na_2CO_3 in 140 ml. of H_2O was allowed to stand overnight at room temperature. Upon cooling and filtering, 3.4 g. (79%) of crude product was obtained. After recrystallization from hot acetone, by chilling, the white crystals melted at 126°.

Anal. Calcd. for $C_{13}H_{10}FNO_2$: C, 67.55; H, 4.37. Found: C, 67.73; H, 4.25.[4]

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[3] F. Krohnke and W. Heffe, *Ber.*, **70B**, 864 (1937).

[4] We wish to thank Dr. J. L. Hartwell of the National Cancer Institute for obtaining these analyses.

DEPARTMENT OF CHEMISTRY
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The Polarizing Effect of Trace Amounts of Antimony(III) on the Electrolytic Oxidation of Arsenic in Acid Solution

BY BERTSIL B. BAKER AND WILLIAM M. MACNEVIN

RECEIVED OCTOBER 10, 1952

In a previous investigation[1] the electrolytic oxidation of arsenic has been shown to proceed with 100% current efficiency in strong acid solution and, more recently, use has been made of this reaction in a coulometric determination of arsenic.[2] During this latter work it was found that the magnitude of the current during the electrolysis did not diminish in a regular fashion as was expected, but instead exhibited the unusual minimum shown in Fig. 1. This paper is concerned with the explanation of this behavior.

It has been shown[3,4] that the current in a 100% current efficient electrolysis conducted at constant electrode potential may be expected to follow the equation $i_t = i_0e^{-tk}$, where i_t is the current at any time t, i_0 the initial current, and k a constant. Integration of this equation[2] gives the area under the curve as equal to $i_0/2.303\ kt$, where i_0 is the intercept and k the slope of the straight line obtained by plotting $\log_{10}$ current *vs.* time. That the current in ordinary primary coulometric determinations does follow such an equation has been demonstrated in the case of the controlled potential reduction of lead,[3] copper,[4] picric acid,[3] and the oxidation of iron.[2] In this latter case agreement with the equation was sufficiently close to allow calculation of the results of a coulometric determination of iron from the integrated equation by determining only the slope and intercept of the log current *vs.* time curve. It was expected that this same technique could be applied to the coulometric determination of arsenic, and it was in attempting to do so that the unusual shape of the electrolysis curve was observed.

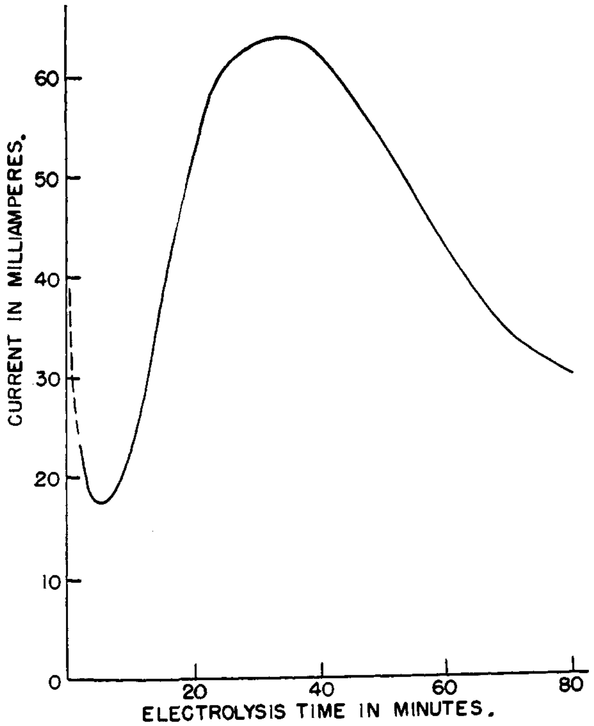

Fig. 1.—A typical minimum in the current–time curve for the electrolytic oxidation of "Analytical Reagent" quality As_2O_3.

Experimental

Apparatus.—The electrolysis cell consisted of two 180-ml. electrolytic beakers sealed together at the bottom by a tube *ca.* 40 mm. long and 20 mm. in diameter containing a medium porosity fritted-glass disk. The anode compartment was stirred with a plastic-coated magnetic stirring bar.

A potentiostat of the design of Lingane[5] was used to provide control of the anode potential to *ca* 0.01 volt.

Current values were recorded automatically by a Leeds and Northrup Model S 40000 Series Micromax Multiple Point Recorder which measured the voltage drop across a resistance in series with the electrolysis cell. The instrument was designed to record about once a minute but during the latter part of this work was modified to record about every 10 seconds.

The electrodes used were "Slomin" platinum gauze electrodes. The cathode area was 75 sq. cm. and the anode 40 sq. cm. by approximate geometric measurement. The actual area was undoubtedly much larger, since the surface was sand-blasted.

Procedure.—When it was found[6] that an oxide film on the anode affects the magnitude of the current in the electrolytic oxidation of arsenic, the anode was pre-polarized at hydrogen evolution to remove any oxide layer. This was done by electrolyzing 1 *M* sulfuric acid between two platinum electrodes for two minutes with a total of four volts applied potential, supplied from two cells of a six-volt storage battery. The cathode in this electrolysis was then used as anode in the oxidation of arsenic.

The catholyte was 100 ml. of 1 *M* sulfuric acid and the anolyte 100 ml. of *ca.* 0.025 *N* arsenic(III) in 1 *M* sulfuric acid, except during the concentration studies. The electrolyses were conducted with a controlled anode potential of either −1.0 or −1.2 volts *vs.* satd. calomel electrode. Slightly higher initial currents were obtained with the higher potential, but the general shape of the curves remained the same.

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[1] W. M. MacNevin and G. L. Martin, THIS JOURNAL, **71**, 204 (1949).

[2] W. M. MacNevin and B. B. Baker, *Anal. Chem.*, **24**, 986 (1950).

[3] J. J. Lingane, THIS JOURNAL, **67**, 1916 (1945).

[4] J. J. Lingane, *Anal. Chim. Acta*, **2**, 584 (1948).

[5] J. J. Lingane, *Ind. Eng. Chem.*, *Anal. Ed.*, **17**, 332 (1945).

[6] B. B. Baker and W. M. MacNevin, THIS JOURNAL, **75**, 1476 (1953).

Results and Discussion

It has been shown previously from coulometric studies[2] that the over-all electrolytic process occurring at −1.0 to −1.2 volts in 1 *M* sulfuric acid solution is the oxidation of arsenic(III) to arsenic(V) with 100% current efficiency. This means that the area under the curve shown in Fig. 1 is correct; it is only the shape of the curve that is anomalous.

The effect of concentration of the arsenic(III) solution on the shape of the electrolysis curve was the first study which gave any hint as to what might be happening. Figure 2 shows this effect. Here it is seen that an extremely dilute solution (0.0009 *N*) gives a normal curve, (the log plot is nearly a straight line), a somewhat more concentrated solution (0.0044 *N*) exhibits a plateau, a still more concentrated solution (0.027 *N*) a minimum, while the most concentrated solution (0.09 *N*) has such a pronounced minimum that it is very difficult to oxidize at all.

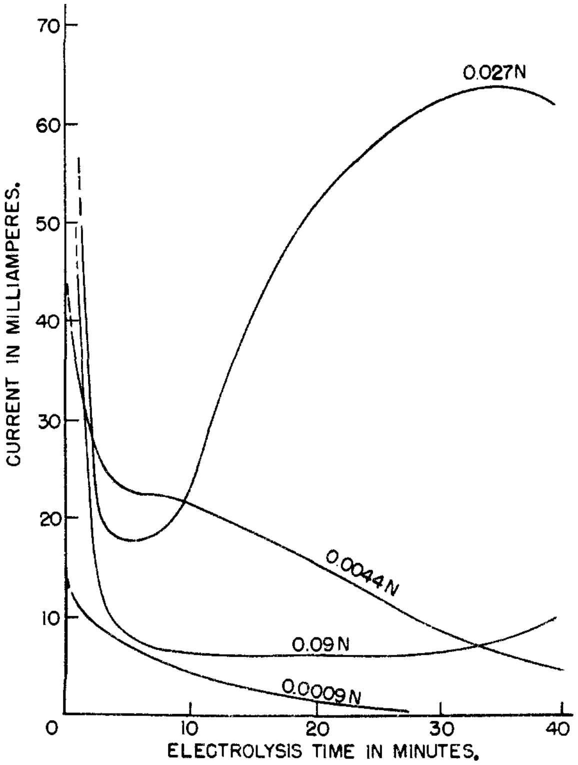

Fig. 2.—Time-current electrolysis curves for the oxidation of solutions of "Analytical Reagent" quality As_2O_3 of various concentrations.

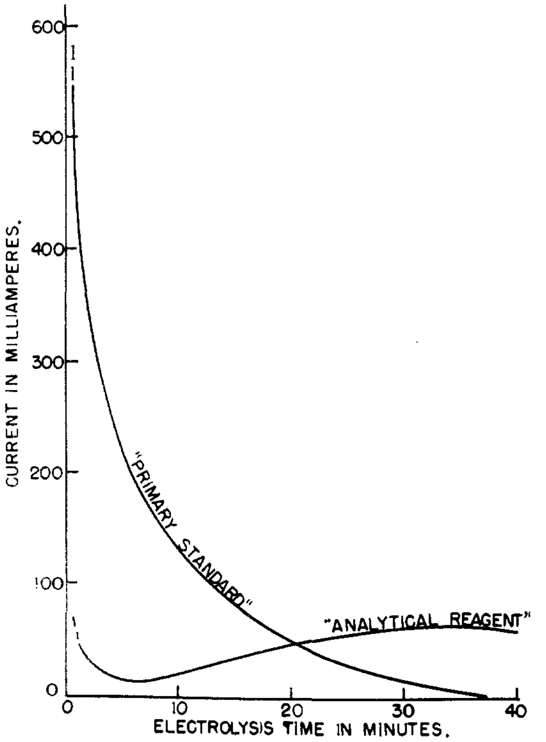

Fig. 3.—Time-current electrolysis curves for the oxidation of solutions of "Analytical Reagent" and "Primary Standard" quality As_2O_3.

This suggested the presence of an interfering impurity. The arsenic solution had been prepared in the usual way by dissolving As_2O_3 in excess potassium hydroxide and then acidifying with sulfuric acid. The potassium hydroxide as a source of impurity was eliminated by preparing a solution by shaking As_2O_3 in water for several days. This solution gave a curve very similar to those prepared with hydroxide, indicating that the impurity must be in the As_2O_3 itself. The As_2O_3 that had been used was Mallinckrodt "Analytical Reagent" quality. Mallinckrodt "Primary Standard" quality is of a higher degree of purity so solutions were prepared using this material. Figure 3 shows current-time curves for the oxidation of two solutions of As_2O_3 identical in every respect except that one was prepared from "Analytical Reagent" As_2O_3 and the other from "Primary Standard" As_2O_3. These results established that an impurity in the As_2O_3 was the cause of the minimum. Lead(II), bismuth(III) and sulfide were added to the "Primary Standard" As_2O_3 solution, but when present in amounts corresponding to the probable amount of impurity (*i.e.*, less than 0.02%) their effect on the curve was negligible. Antimony(III) and tin(II), however, were found to produce the minimum quite readily. Of the two, antimony had a much greater effect. Electrolysis curves resulting after the addition of antimony(III) to the arsenic solution prepared from "Primary Standard" As_2O_3 are shown in Fig. 4.

An inquiry was made of the Mallinckrodt Chemical Works about the differences between these two grades of As_2O_3. They furnished spectrographic analyses of each, indicating that the principal difference was the presence of a detectable amount of antimony (estimated 0.1 to 0.01%) in the "Analytical Reagent" quality.

The current-time curve for the oxidation of the "Primary Standard" As_2O_3 nearly follows the $i_{t0} = i_0e^{-kt}$ relation. Figure 5 is a log current *vs.* time plot. It was not established whether the deviation during the first five minutes was due to a trace of antimony(III) remaining in the "Primary Standard" As_2O_3 or to another cause.

One possible explanation for the effect of antimony is that a layer of higher oxide, perhaps Sb_2O_4, may form on the surface of the electrode rendering it passive to the oxidation of arsenic. Some evi-

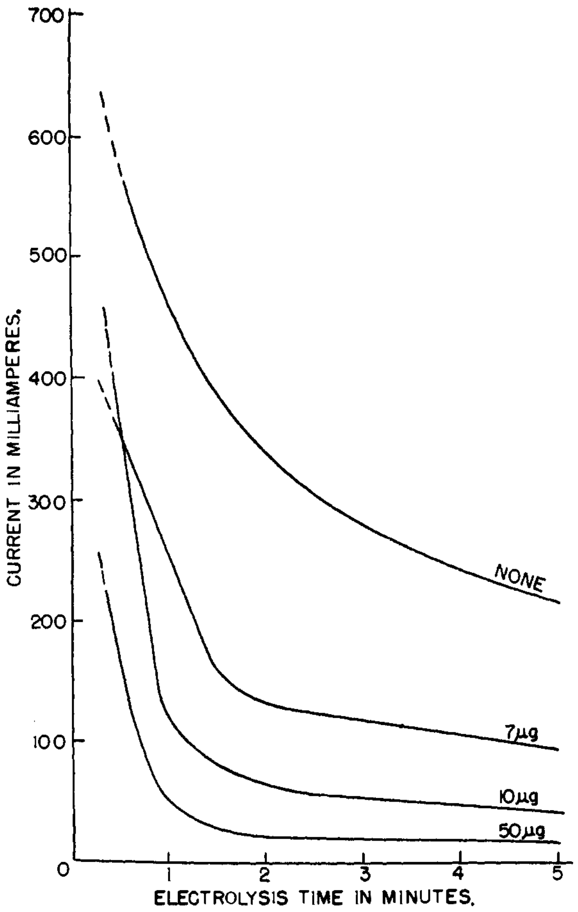

Fig. 4.—The effect on current-time curves of the addition of microgram quantities of Sb(III) to solutions of "Primary Standard" quality As_2O_3.

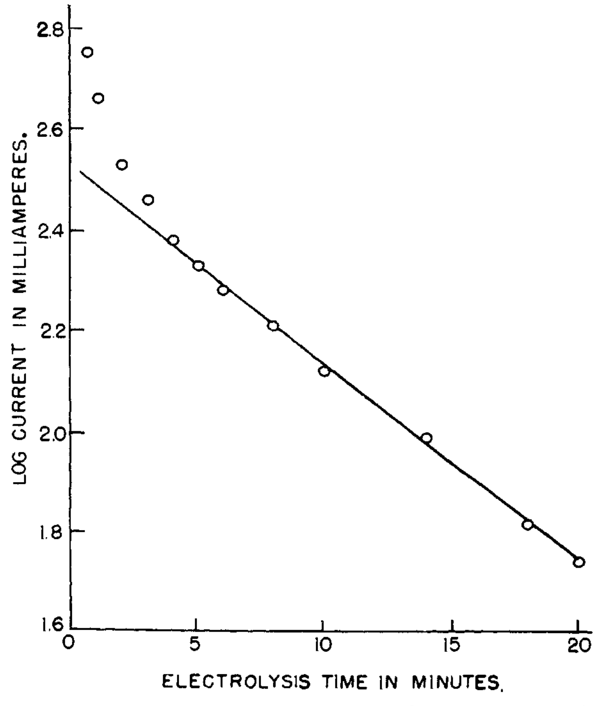

Fig. 5.—A log current *vs.* time curve for the electrolytic oxidation of "Primary Standard" quality As_2O_3.

dence to support this may be drawn from Fig. 4 which shows the current lowering to be very great for amounts of antimony up to about ten micrograms, and that then additional amounts cause relatively less change. Ten micrograms is of the order of magnitude needed for the formation of a monomolecular layer of oxide over the surface of the electrode. Two other experimental observations are in general accord with this theory. These are, that the addition of antimony(V) to the solution has no effect on the electrolysis curve, and that the antimony(III) minimum does not appear at all when the electrolysis is carried out in molar sodium hydroxide. The absence of the minimum in alkaline solution could be the result of the disproportionation of Sb_2O_4 which Latimer[7] reports to be slow in acid but rapid in alkaline solution.

It was further observed that if, after the acid solution electrolysis had run several minutes, the current were turned off and the electrode allowed to stand in the solution a much higher current was observed on resumption of electrolysis. This could be the result of the slow disproportionation and dissolution of the Sb_2O_4 layer from the surface of the electrode. The effect is represented in Fig. 6.

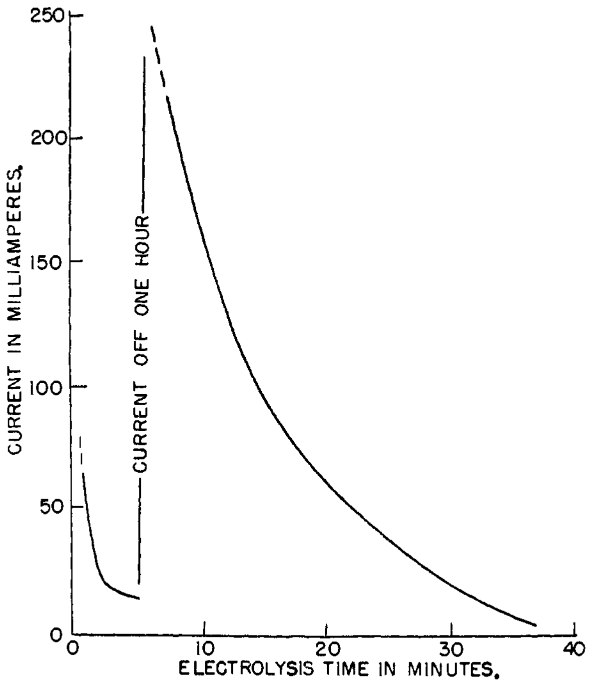

Fig. 6.—Effect of current interruption on the time-current curve for the oxidation of "Analytical Reagent" quality As_2O_3.

Acknowledgment.—This research was supported in part from funds granted by The Ohio State University Research Foundation to the University for aid in fundamental research and in part by a grant from the E. I. du Pont de Nemours and Company.

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[7] W. M. Latimer, "Oxidation Potentials," 2nd edition, Prentice-Hall, Inc., New York, N. Y., 1952, p. 119.

The Effect of Pre-polarization of a Platinum Anode on the Current Obtained in the Controlled Potential Oxidation of Iron and of Arsenic

By Bertsil B. Baker and William M. MacNevin

Received October 10, 1952

In the course of some experiments on the electrolytic oxidation of arsenic in acid solution[1] the authors experienced difficulty in obtaining the same current values in successive electrolyses under supposedly the same conditions. A principal cause was found to be the presence of a variable amount of oxide on the surface of the smooth platinum anode employed in the electrolysis. It was then found that the pre-treatment of the electrode, particularly with regard to hydrogen or oxygen evolution, could cause at least a tenfold variation in currents obtained in the oxidation of both iron and arsenic. Although various investigators[2,3,4] have demonstrated the presence of platinum oxides on electrodes and mention has been made of the effect of prepolarization on current efficiency in certain electrolyses,[5] iron and arsenic are not among these, nor have there been any studies made at constant potential. This paper is therefore offered to present data pertaining to these two cases and to call attention to the presence of a phenomenon which the authors feel may be of more common occurrence and significance than is generally recognized.

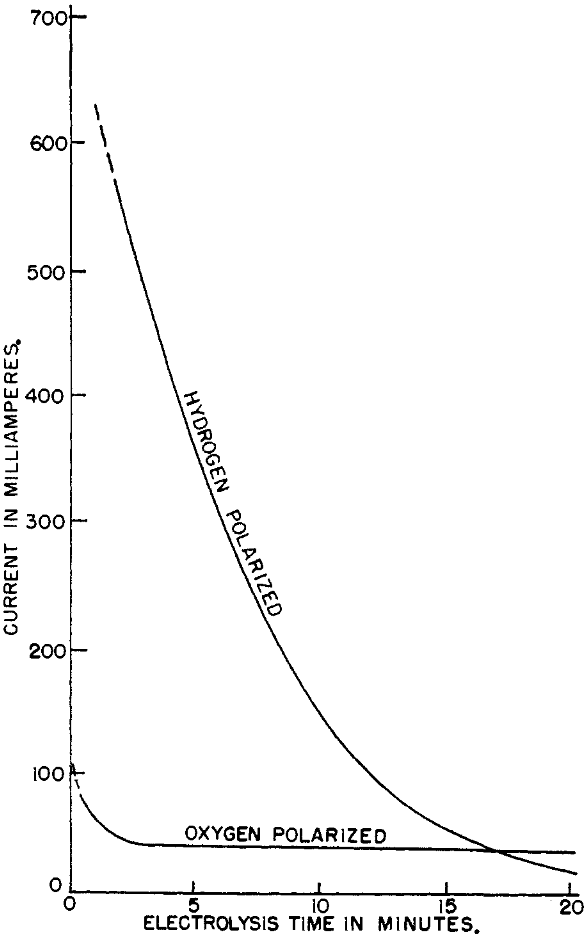

Fig. 1.—Effect of pre-polarization on current obtained in electrolytic oxidation of arsenic.

Slomin-type platinum electrodes, a divided compartment cell, an automatic potentiostat, and an automatic recorder were used. These have all been described previously.[1,6] The iron oxidations were conducted at an anode potential of −0.7 volt and the arsenic at −1.0 volt *vs.* satd. calomel electrode. The electrolyte was 1 *M* sulfuric acid approximately 0.025 *N* in iron or arsenic. Unless otherwise stated the potential was applied before the anode was lowered into the solution so that electrolysis began immediately, and before each run the resistances in the potentiostat were manually set at the position that previous runs had shown would give the desired potential at the beginning of the electrolysis. Pre-polarization was carried out in 1 *M* sulfuric acid for two minutes with a total applied potential of 4.0 volts, delivered from two cells of a 6-volt storage battery. This gave quite vigorous gas evolution, some heat, and a maximum

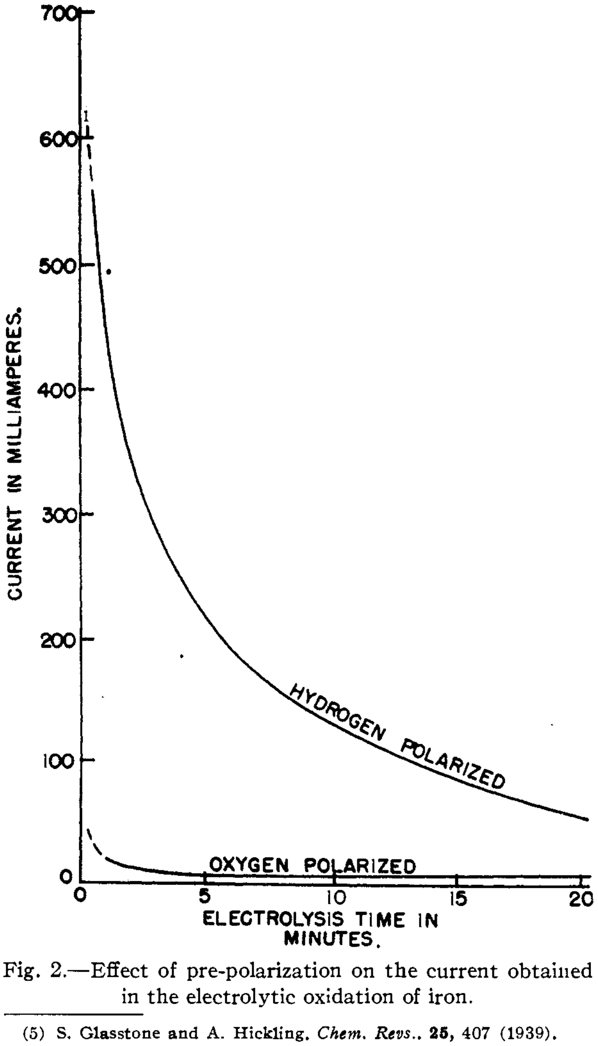

Fig. 2.—Effect of pre-polarization on the current obtained in the electrolytic oxidation of iron.

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[1] B. B. Baker and W. M. MacNevin, This Journal, **75**, 1473 (1953).

[2] J. D. Pearson and J. A. V. Butler, *Trans. Faraday Soc.*, **34**, 1163 (1938).

[3] A. Hickling, *ibid.*, **41**, 333 (1945).

[4] S. E. S. El Wakkad and S. H. Emara, *J. Chem. Soc.*, 461 (1952).

[5] S. Glasstone and A. Hickling, *Chem. Revs.*, **25**, 407 (1939).

[6] W. M. MacNevin and B. B. Baker, *Anal. Chem.*, **24**, 986 (1952).

polarization effect. It was found that an electrode either anodically or cathodically polarized in this fashion remained in its same condition after several hours of standing in 1 *M* sulfuric acid and was not changed even by several minutes in hot concentrated nitric acid. By "remaining in its same condition" is meant that the electrode would exhibit the same behavior in a subsequent electrolysis, which was the only criterion we could apply as to the state of the surface of the electrode.

Figure 1 shows the subsequent effect in an arsenic oxidation of prior hydrogen and oxygen pre-polarization treatment of the platinum anode. Figure 2 shows similar behavior in an iron oxidation.

It was further observed (Fig. 3) that if an oxygen pre-polarized electrode was allowed to stand for one hour in the arsenic solution before beginning the electrolysis the electrode slowly reverted to a condition similar to that of a hydrogen pre-polarized electrode. The most likely explanation is that the arsenic(III) reduces the platinum oxide (probably (PtO) and gives a clean platinum surface. A similar process occurs if the electrode stands in the iron solution before the electrolysis is begun but the reaction is quite rapid, about 10 to 20 seconds sufficing for the complete removal of the oxide. The speed of this reaction probably accounts for this effect not having been observed before in iron oxidations. However, it should be noted that, as Fig. 2 indicates, if the potential is applied and maintained, then the current remains low throughout the entire electrolysis. This means that the iron solution cannot reduce the oxide while the potential is applied and oxidation is occurring at the electrode.

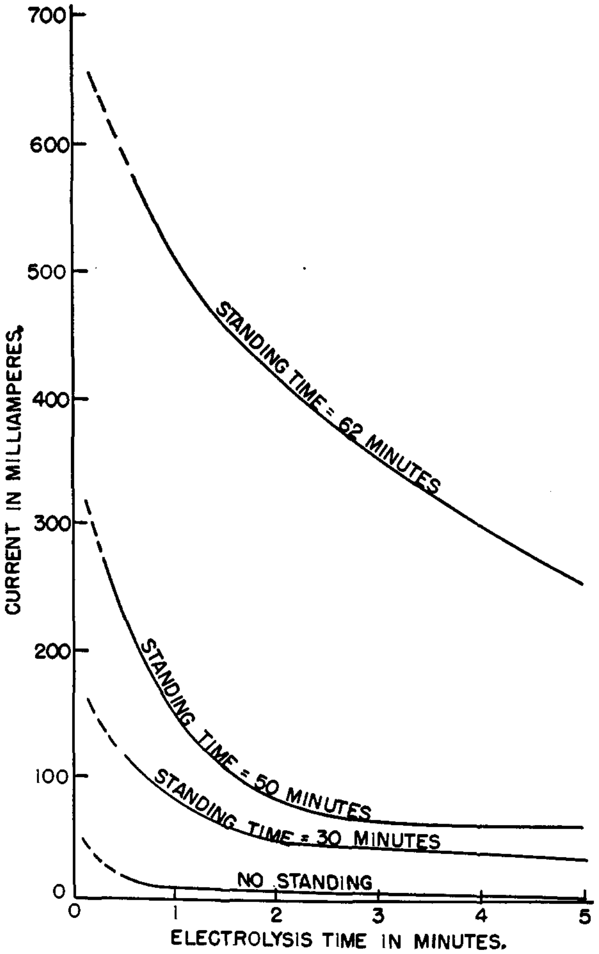

Fig. 3.—Effect of oxygen pre-polarized electrode standing in As(III) solution prior to electrolysis.

Acknowledgment.—This research was supported in part from funds granted by The Ohio State University Research Foundation to the University for aid in fundamental research and in part by a grant from the E. I. du Pont de Nemours and Company.

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
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X-Ray Examination of Polychlorotrifluoroethylene[1]

BY H. S. KAUFMAN

RECEIVED OCTOBER 24, 1952

The X-ray investigation of the structure of polychlorotrifluoroethylene has been undertaken in order to obtain an understanding of the behavior of the polymer in terms of its structural parameters. The polymer, known commercially as KEL-F, is of interest because of its chemical inertness, low solubility, high softening point, and satisfactory electrical and mechanical properties.

The development of crystallinity at temperatures below the first order transition temperature at 211° has been investigated by X-ray methods. The data supplement those obtained by Price[2] using optical methods.

Debye–Scherrer diagrams of the polymer were obtained using crystal monochromatized CuKα radiation and a flat camera. The patterns of unoriented polycrystalline samples showed one strong line at about 5.5 Å. and several other relatively weak lines at smaller spacings. A high resolution Geiger counter spectrometer was used to study the fine structure that had been observed in some of the Debye–Scherrer patterns of highly crystalline samples.

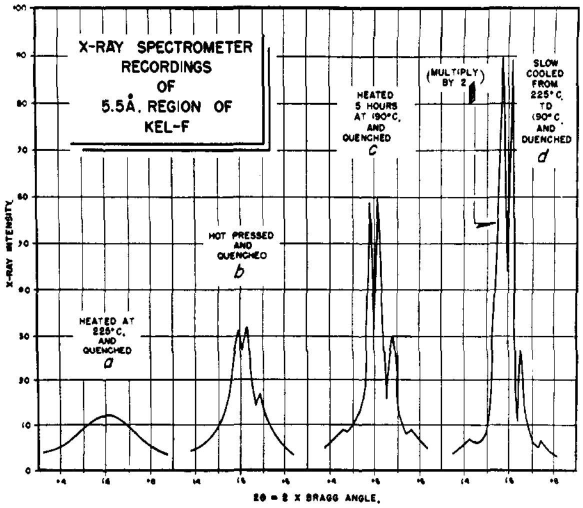

Fig. 1.

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(1) This paper was presented at the Diamond Jubilee Meeting of the American Chemical Society held in New York in September, 1951.

(2) **F. P. Price**, THIS JOURNAL, **74**, **311** (1952).

Typical spectrometer patterns of the 5.5 Å. region of samples of varying degrees of crystallinity are presented in Fig. 1. The quick quenching to a low temperature of polymer heated above its transition temperature results in a glass-clear sample which gives a low intensity, broad diffraction line characteristic of a relatively disordered amorphous structure (Fig. 1a). Extensive crystallinity with increasing opacity is developed by lengthening the residence time of the polymer at temperatures between 190° and the transition temperature. The increase in crystallinity is accompanied by a splitting of the broad amorphous line into two strong and relatively sharp lines with less intense lines at the side (Figs. 1b, c, d).

The influence of molecular weight on the development of crystallinity was investigated by studying the effect of the various thermal treatments noted in Fig. 1 on samples with molecular weights of 50,000, 75,000 and 100,000, respectively. For a given heat treatment, the degree of crystallinity developed varied inversely with molecular weight.

Fiber diagrams were obtained from highly crystallized and oriented fibers prepared by the hot drawing of the polymer. The fiber patterns varied with degree of orientation. Arcs which developed on slight orientation split in two at the equator as the extent of orientation was increased and finally, in the most oriented sample, sharp spots were formed. The spacings and relative intensities of these spots were in exact correspondence with the 5.5 Å. region lines observed in the spectrometer curves of the most crystalline sample.

Measurement of the lateral spacings along the row lines of the fiber diagrams and of the lines observed in the Debye–Scherrer patterns gave a series of spacings, beginning with 5.6 Å., which were in the inverse ratios of $1:\sqrt{3}:\sqrt{4}:\sqrt{7}:\sqrt{9}$. These ratios, being characteristic of the hexagonal system, suggested that the polymer chains were packed in hexagonal unit cells. One dimension of the unit cell was calculated from these data and found to be 6.5 Å. The repeat distance along the fiber axis was determined to be 35 Å. from measurements of the layer-line separation of the spots. These data established the unit cell to be hexagonal, with the dimensions A = 6.5 Å. and C = 35 Å.

One structure which accounts for the extraordinarily long fiber spacing of 35 Å. is a spiral chain arranged so that the spiral starts to repeat itself after approximately 14 monomer units. This structure is similar to that which has been assigned to the spiral of polyisobutylene[3] and of Teflon.[4] A planar zig-zag chain such as in polyvinyl chloride or polyethylene is ruled out because it requires a fiber axis spacing of about 5 Å.

On the basis of this assumed structure, the density of the polymer may be calculated using the equation

$$d = \frac{1.65 \times M \times n}{V}$$

where

M = molecular weight of monomer unit = 116.5

n = no. of monomer units per unit cell = 14

V = volume of unit cell = 1290 Å.[3]

The calculated value is 2.10 g./cc, in agreement with the value of 2.12 g./cc. determined experimentally by the flotation method using a solution of *sym*-tetrabromoethane and diethyl phthalate.

Acknowledgments.—The author is grateful to Drs. E. Solomon, I. Fankuchen and D. Harker for their helpful comments and suggestions.

M. W. KELLOGG CO.
NEW YORK, N. Y.

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[3] C. S. Fuller, C. J. Frosch and N. R. Pape, THIS JOURNAL, **62**, 1909 (1940).

[4] R. H. H. Pierce, W. M. D. Bryant and J. F. Whitney, presented at National A. C. S. Meeting, Buffalo, N. Y., March, 1952.

Dissociation Constants of Substituted Ethylenediamines[1]

BY FRED BASOLO, R. KENT MURMANN AND YUN TI CHEN

RECEIVED NOVEMBER 6, 1952

In the course of investigating the stepwise formation constants of numerous metal ammines, it was necessary to determine the acid–base dissociation constants or "hydrolysis" constants of the amines. These dissociation constants have been reported for the N-alkylethylenediamines[2] and this paper gives an account of analogous determinations for several NN′-dialkylethylenediamines and C-substituted ethylenediamines.

Experimental

Reagents.—NN′-diMeen, NN′-diEten, NN′-di-*n*-Pren and NN′-di-*n*-Buen[3] were prepared by the method of Schneider.[4] NN′-di-*i*-Pren was prepared by a modification of the procedure of Zienty,[5] using ethylene dibromide and isopropylamine. One mole of ethylene dibromide was refluxed with five moles of isopropylamine for 24 hours. The mixture became almost solid with crystals. An excess of 20% sodium hydroxide solution was added and the mixture distilled over solid sodium hydroxide. The amine was then distilled over sodium; yield 60%.

Both *dl*-bn and *m*-bn were prepared by reduction of dimethylglyoxime with platinum and hydrogen in a Parr bomb (80% yield)[6] and also by reduction with Raney nickel–aluminum alloy and aqueous alkali (41% yield).[7] The second method was found to be the most convenient in spite of the low yield because it could be carried out on a larger scale. The *meso* and *racemic* bn's were separated by fractional crystallization of the dihydrochlorides from methyl alcohol. The *racemic* form is about eight times more soluble than the *meso* form at room temperature. The free amines were liberated by the reaction of the calculated amount of sodium methoxide with the dihydrochlorides in absolute alcohol, followed by distillation under reduced pressure.

iso-Bn was prepared by the reduction of α-aminobutyronitrile with lithium aluminum hydride in anhydrous ether. Eighty-four grams of α-aminoisobutyronitrile in 200 ml. of anhydrous ether was added dropwise, over a period of two hours, to a well-stirred slurry of 76 g. of $LiAlH_4$ and 2 l. of

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[1] This investigation was supported by a grant-in-aid from the National Institutes of Health; Grant No. G-3239.

[2] F. Basolo and R. K. Murmann, THIS JOURNAL, **74**, 2373 (1952).

[3] The diamines discussed here are designated as follows: NN′-diMeen = N,N′-dimethylethylenediamine; NN′-diEten = N,N′-diethylethylenediamine; NN′-di-*n*-Pren = N,N′-di-*n*-propylethylenediamine; NN′-di-*i*-Pren = N,N′-di-*i*-propylethylenediamine; NN′-di-*n*-Buen = N,N′-di-*n*-butylethylenediamine; pn = 1,2-diaminopropane (propylenediamine); *dl*-bn = *rac*-2,3-diaminobutane; *m*-bn = *meso*-2,3-diaminobutane; *iso*-bn = 1,2-diaminoisobutane; TetraMeen = 2,3-diamino-2,3-dimethylbutane; *dl*-stien = *rac*-1,2-diphenylethylenediamine; *m*-stien = *meso*-1,2-diphenylethylenediamine.

[4] P. Schneider, *Ber.*, **28**, 3074 (1895).

[5] F. B. Zienty, THIS JOURNAL, **68**, 1388 (1946).

[6] L. B. Clapp, Ph.D. Thesis, University of Illinois, 1941.

[7] F. H. Dickey, W. Fickett and H. J. Lucas, THIS JOURNAL, **74**, 944 (1952).

anhydrous ether. The mixture was stirred overnight at room temperature and then decomposed by the addition of 50 ml. of water, 40 ml. of 20% sodium hydroxide solution and 150 ml. of water, in that order, with cooling. The solid was removed by filtration and the ether solution dried over anhydrous sodium sulfate. Fractional distillation of this solution gave 30 g. (34%) of *iso*-bn. Another 10–15 g. of the amine was obtained from the solid by digesting it with hot benzene and distilling the extract.

Anal. Calcd. for the dihydrochloride, $C_4H_{12}N_2Cl_2$: Cl, 44.0. Found: Cl, 43.7.

TetraMeen could not be prepared from the reaction of 2,3-dibromo-2,3-dimethylbutane with either aqueous ammonia or liquid ammonia. Likewise it was found that tetramethylsuccinamide reacted with sodium hypobromite in water to give only complex mixtures from which no TetraMeen could be isolated. TetraMeen was finally prepared by the reduction of 2,3-dinitro-2,3-dimethylbutane[8] with zinc and concentrated hydrochloric acid[9] (40% yield). Catalytic reduction with platinum or Raney nickel and hydrogen gave very poor yields of impure product.

The synthesis of *m*-stien involved the condensation of benzaldehyde with liquid ammonia to yield hydrobenzamide which was rearranged to amarine by heating at 130° for five hours.[10] Amarine was acetylated by refluxing with acetic anhydride and sodium acetate for four hours. Hydrolysis of the *meso*-N-benzoyl-N′-acetyl-1,2-diphenylethylenediamine with 50% (by volume) sulfuric acid[11] and treatment with sodium hydroxide gave solid *m*-stien, which was recrystallized several times from water to give a pure product.

rac-Stilbenediamine was prepared by rearranging amarine to isoamarine by heating four moles of amarine with five moles of sodium hydroxide in 150 ml. of water and 800 ml. of diethylene glycol to boiling for one hour. The isoamarine was then acetylated and hydrolyzed as with amarine and pure *dl*-stien was obtained after three crystallizations from high boiling petroleum ether.

The boiling points or melting points of the final purified amines shown in Table I are in good agreement with the values reported in the literature.

TABLE I

NN′-DI-ALKYLETHYLENEDIAMINES ($RNHCH_2CH_2NHR$)

R	B.p., °C.
Me	118-119[4]
Et	148-150[4]
n-Pr	186-188[a]
i-Pr	171-171.5
n-Bu	111-113 (10 mm.)[a]

C-SUBSTITUTED ETHYLENEDIAMINES ($NH_2CRR'CR''R'''NH_2$)

Amine	B.p., °C.	M.p., °C.
pn	118-119[b]	
dl-bn	44-45 (25 mm.)[7]	
m-bn	46-48 (25 mm.)[7]	
iso-bn	36-38 (15 mm.)[11]	
TetraMeen	147-148[9]	97-98[9]
dl-stien		80-82[10]
m-stien		119-120[10]

[a] J. A. King and F. H. McMillan, THIS JOURNAL, 68, 1774 (1946). [b] Beilstein, "Organische Chemie," Band IV, p. 257.

Preparation of Solutions and Titrations.—The amines were diluted with water until they were 1.5 to 5 molar and then standardized against standard acid by means of conductometric and *p*H titrations. Because of the low solubility of NN′-di-*n*-Buen, *dl*-stien, and *m*-stien, they were dissolved in 15, 50 and 50% by volume dioxane–water solutions, respectively. The primary standard for all acid–base titrations was a sample of 99.96% potassium hydrogen phthalate obtained from the Bureau of Standards.

The constant ionic strength nitric acid solution containing barium nitrate was made in the same manner as previously described.[2] All measurements were made in the presence of 0.05 *M* $Ba(NO_3)_2$ and 0.50 *M* KNO_3 except *dl*- and *m*-stien which were titrated against a standard perchloric acid solution containing 0.005 *M* $Ba(ClO_4)_2$ in 50% dioxane–water. The solutions were maintained at constant temperature by means of a constant temperature bath at 25 ± 0.1° and by an intimate mixture of ice and water at 0 ± 0.1°. A Beckman *p*H meter model G was standardized against Beckman standard buffers at a *p*H of 4.00 and 7.00 before each run. With solutions containing 50% dioxane, a calibration curve was made to correct for the change in activity coefficient of the hydrogen ion in a solvent of different dielectric constant. No such correction was necessary for the NN′-di-*n*-Buen because the final solutions contained less than 1% of dioxane.

With each amine, one complete titration curve was made and a series of constant values obtained for pK_1 and pK_2. In each case either another titration was made or two separate solutions were made one of which fell in the first dissociation constant range and the other in the second dissociation range. The constants were checked by measuring the respective *p*H's. The constants calculated from these solutions agreed with those obtained from the titration within ±0.01 *pK* unit.

The dissociation constants at 0 and 25° along with the heats of neutralization are summarized in Tables II and III. A graphic representation of these *pK* values is shown in Figs. 1 and 2.

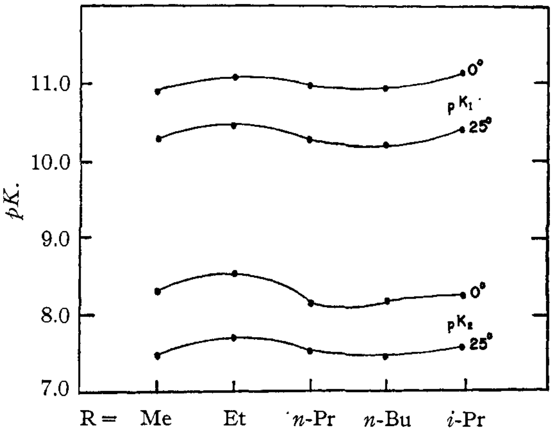

Fig. 1.—Dissociation constants of N,N′-dialkylethylenediamines, $RNHCH_2CH_2NHR$.

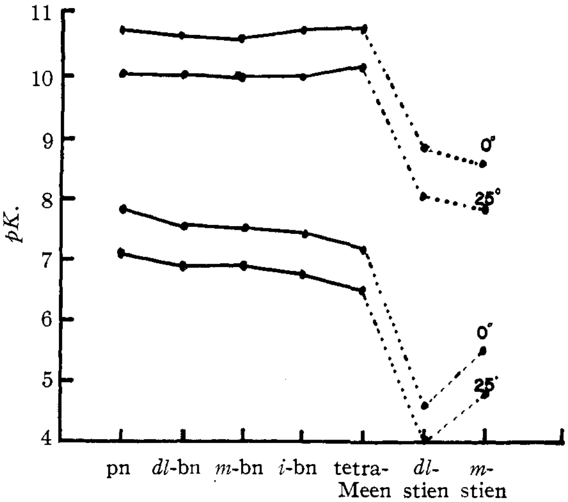

Fig. 2.—Dissociation constants of C-substituted ethylenediamines: —, water; - - -, 50% dioxane–water.

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[8] L. W. Siegle and H. B. Hass, *J. Org. Chem.*, 5, 100 (1940).

[9] J. Bewad, *Ber.*, 39, 1233 (1906).

[10] I. Lifschitz and J. G. Bos, *Rec. trav. chim.*, 59, 173 (1940); O. F. Williams, Ph.D. Thesis, University of Illinois (1952).

[11] W. H. Mills and T. H. H. Quibell, *J. Chem. Soc.*, I, 843 (1935).

Results

The acid–base dissociation constants of the N,N′-dialkylethylenediamines are nearly the same from methyl to *n*-butyl with a slight rise in pK_1 and pK_2 with NN′-di-Eten. This same maximum was noted previously for pK_2 of the N-alkylethylenediamine series[2] at N-ethylethylenediamine, although it was not found in pK_1. As is the case in the N-alkylethylenediamine series, NN′-di-*i*-Pren is a stronger base than NN′-di-*n*-Pren. It is likewise noteworthy that although the pK_2 values of the N,N′-dialkylethylenediamines are similar to the pK_2 values of the N-alkylethylenediamines, these are not the same.

TABLE II

DISSOCIATION CONSTANTS AND HEATS OF NEUTRALIZATION OF N,N′-DIALKYLETHYLENEDIAMINES

Amine	pK_1 0°	pK_1 25°	pK_2 0°	pK_2 25°	ΔH, kcal. ΔH_1	ΔH, kcal. ΔH_2
NN′-diMeen[a]	8.30	7.47	10.89	10.29	−12.4	− 8.9
NN′-diEten	8.53	7.70	11.06	10.46	−12.4	− 8.9
NN′-di-*n*-Pren	8.14	7.53	10.97	10.27	− 9.1	−10.4
NN′-di-*n*-Buen	8.18	7.46	10.93	10.19	−10.7	−11.0
NN′-di-*i*-Pren	8.26	7.59	11.12	10.40	−10.0	−10.7

[a] 7.28, 10.06 (No specific temperature was given). Irving, Paper No. 4, "A Discussion on Coördination Chemistry," Butterwick Research Laboratories, I.C.I., Sept. 21–2, 1950.

TABLE III

DISSOCIATION CONSTANTS AND HEATS OF NEUTRALIZATION OF C-SUBSTITUTED ETHYLENEDIAMINES

Amine	pK_1 0°	pK_1 25°	pK_2 0°	pK_2 25°	ΔH, kcal. ΔH_1	ΔH, kcal. ΔH_2
pn[a]	7.81	7.13	10.76	10.00	−10.1	−11.3
dl-bn	7.60	6.91	10.69	10.00	−10.3	−10.3
m-bn	7.55	6.92	10.63	9.97	− 9.4	− 9.8
iso-bn	7.41	6.79	10.74	10.00	− 9.2	−11.0
TetraMeen	7.18	6.56	10.73	10.13	− 9.2	− 8.9
dl-stien (50% dioxane)	4.60	3.95	8.85	8.09	− 9.7	−11.3
m-stien (50% dioxane)	5.55	4.78	8.59	7.85	−11.6	−11.0

[a] 7.00, 9.78 (30°, 0.5 KNO_3). Carlson, McReynolds and Verhoek, THIS JOURNAL, **67**, 1334 (1945).

Substitution of methyl groups in the carbons of an ethylenediamine skeleton only slightly decreases the base strength of the amine. However, substitution of phenyl groups, as in stilbenediamine, appears to decrease the base strength but it must be remembered that much of this decrease may be due to a change in solvent. Little difference was noted between *dl*-bn and *m*-bn although the former was slightly more basic, while pK_1 of *dl*-stien is slightly larger than that for *m*-stien and the reverse is true for their pK_2 values.

The heats of neutralization are in the range of −9 to −12 kcal. which is slightly higher than that found for the N-alkylethylenediamines.

DEPARTMENT OF CHEMISTRY
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$\Delta^{5,7}$-Steroids. XV.[1] $\Delta^{3,5,7}$-Cholestatriene-3-ol Acetate

BY SEYMOUR BERNSTEIN, MILTON HELLER AND JAMES H. WILLIAMS

RECEIVED SEPTEMBER 25, 1952

In the previous paper of this series, there was described the preparation of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate by the treatment of $\Delta^{4,7}$-cholestadiene-3-one with acetic anhydride and pyridine. The physical constants [m.p. 101.5–103°; $\lambda_{\max}^{\text{abs. alc.}}$ 302.5–303, 315 and 330.5 mμ, ε17900, 22600, and 16200, respectively; $[\alpha]^{25}\mathrm{D}$ −147° (chloroform)] of this preparation were strikingly different than those reported by Dauben and co-workers,[2] who prepared this enol acetate from $\Delta^{4,6}$-cholestadiene-3-one with acetic anhydride and acetyl chloride. In view of the reported conversion of $\Delta^{4,6,22}$-ergostatriene-3-one with acetic anhydride and acetyl chloride to $\Delta^{2,4,6,22}$-ergostatetraene-3-ol acetate (64% yield),[3] it was proposed[1] that the California preparation may have consisted of mixed crystals of $\Delta^{2,4,6}$- and $\Delta^{3,5,7}$-cholestatriene-3-ol acetates.

We now wish to report that, in our hands, treatment of the $\Delta^{4,6}$-3-ketone with acetic anhydride and acetyl chloride gave $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (27% yield), identical in *all* respects with the compound prepared from the $\Delta^{4,7}$-3-ketone. A spectral analysis of the initial mother liquors obtained on the recrystallization of the enol acetate indicated the presence of only starting material (?), and no $\Delta^{3,5,7}$- or $\Delta^{2,4,6}$-enol acetates. This may be accounted for by incomplete reaction, or by unintentional hydrolysis of any enol acetate present. Whether or not a $\Delta^{4,6}$-3-ketone under these conditions gives rise to a mixture of enol acetates remains unsolved.

To substantiate further this method of preparing a $\Delta^{3,5,7}$-enol acetate from a $\Delta^{4,6}$-3-ketone, $\Delta^{4,6}$-androstadiene-17β-ol-3-one benzoate was transformed into $\Delta^{3,5,7}$-androstatriene-3,17β-diol-3-acetate-17-benzoate.

Finally, mention should be made of a pertinent optical rotational analysis. It is known that if C-17 "vicinal action" is absent, a compound with an "ergosterol" side chain will have a specific rotation of about 20° ($\Delta[M]\mathrm{D}$ 78°) *more negative* than the corresponding "cholesterol" compound.[4] An examination of the rotations of the four compounds compiled in Table I reveals gross irregularities which unequivocally indicate "vicinal action." These anomalies may be explainable by the suggestion of Barton and Cox[5] of a possible qualitative correlation between anomalies and the ultraviolet absorption spectra of the compounds.

TABLE I

ROTATIONAL ANALYSIS

Compound	$[\alpha]\mathrm{D}$ ($CHCl_3$)	$\Delta[\alpha]\mathrm{D}$
$\Delta^{4,7}$-Cholestadiene-3-one	+33°[a]	...
$\Delta^{4,7,22}$-Ergostatriene-3-one	−12[a]	45°
$\Delta^{3,5,7}$-Cholestatriene-3-ol acetate	−147,[a] −145[b]	...
$\Delta^{3,5,7,22}$-Ergostatetraene-3-ol acetate	−144[a]	0

[a] See ref. 1. [b] This work.

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[1] Paper XIV, R. Antonucci, S. Bernstein, M. Heller and J. H. Williams, *J. Org. Chem.*, **17**, 1446 (1952).

(2) W. G. Dauben, J. F. Eastham and R. A. Micheli, THIS JOURNAL, **73**, 4496 (1951): m.p. 91–93°, $\lambda_{\max}^{\text{alc.}}$ 305, 316 and 330 mμ, ϵ_{316} 20,000; $[\alpha]^{25}\mathrm{D}$ −69° (chloroform).

(3) I. M. Heilbron, T. Kennedy, F. S. Spring and G. Swain, *J. Chem. Soc.*, 869 (1938).

(4) S. Bernstein, W. J. Kauzmann and E. S. Wallis, *J. Org. Chem.*, **6**, 319 (1941).

(5) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

Experimental[6]

$\Delta^{3,5,7}$-Cholestatriene-3-ol Acetate.—A solution of 200 mg. of $\Delta^{4,6}$-cholestadiene-3-one[7] in 10 ml. of acetic anhydride and 20 ml. of acetyl chloride was refluxed for 6 hours, and evaporated *in vacuo*. The residue was treated with methanol which in turn was removed by evaporation *in vacuo*. The methanol treatment was repeated. One recrystallization from methanol afforded 0.18 g., m.p. 91–95°; $\lambda_{\max}^{\text{abs. alc.}}$ 302–303, 316 and 331 mμ, ϵ13000, 15700 and 11000, respectively (59% "*spectroscopic*" yield based on ϵ_{316} 22000). Three further recrystallizations from methanol yielded 60 mg. (27% yield) of pure enol acetate, m.p. 101–102°; $\lambda_{\max}^{\text{abs. alc.}}$ 302.5, 316 and 331 mμ, ϵ 17300, 21900 and 15300, respectively; $[\alpha]^{27}\text{D}$ −145° (7.2 mg., αD −0.51°). The m.p. was undepressed on admixture with the sample prepared from the $\Delta^{4,7}$-3-one. The infrared spectra were identical in all respects.

The first three mother liquors were combined, and evaporated *in vacuo* and gave an oily residue, $\lambda_{\max}^{\text{abs. alc.}}$ 284–287 mμ (starting material?).

$\Delta^{3,5,7}$-Androstatriene-3,17β-diol-3-acetate-17-benzoate.—To a solution of 0.61 g. of $\Delta^{4,6}$-androstadiene-17β-ol-3-one benzoate[8] in 2 ml. of toluene was added 7 ml. each of acetic anhydride and acetyl chloride. The mixture was refluxed for 4 hours, and was worked-up as above; wt. 0.16 g. (from methanol), m.p. 154–156°; $\lambda_{\max.}^{\text{abs. alc.}}$ 228, 302, 314 and 329 mμ, ϵ17600, 18200, 22000 and 15500, respectively, $[\alpha]^{27}\text{D}$ −71.4° (16 mg., αD −0.57°); 24% yield.

Anal.[9] Calcd. for $C_{28}H_{32}O_4$ (432.54): C, 77.75; H, 7.46. Found: C, 77.53; H, 7.69.

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(6) All m.ps. are uncorrected, and were determined with uncalibrated Anschütz thermometers. Optical rotations were performed by solution of the sample in chloroform to make a 2 ml. solution, and were determined in a 1-dm. semi-micro tube.

(7) A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1719 (1946).

(8) C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946).

(9) We wish to thank Mr. Samuel S. Modes for the microanalysis.

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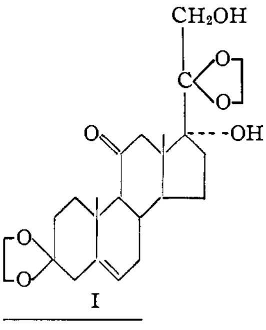
Steroidal Cyclic Ketals. IV.[1] The Conversion of 11-Keto- to 11α-Hydroxysteroids. The Preparation of 11-*Epi*-hydrocortisone, and Δ^4-Androstene-11α-ol-3,17-dione

BY SEYMOUR BERNSTEIN, RUDDY LITTELL AND JAMES H. WILLIAMS

RECEIVED OCTOBER 27, 1952

We have recently reported[1] that reduction of the diethylene ketal of cortisone (Δ^5-pregnene-17α,21-diol-3,11,20-trione-3,20-di-ethylene ketal) (I) in tetrahydrofuran with excess lithium aluminum hydride in ether produced not only the expected 11β-hydroxy compound (di-ethylene ketal of hydrocortisone) (58% yield), but also the 11α-hydroxy-compound (di-ethylene ketal of 11-*epi*-hydrocortisone) (II) (8% crude yield). Acid hydrolysis of the latter afforded 11-*epi*-hydrocortisone. This constituted the first time the 11α-epimer has been isolated and characterized in such a reduction. Moreover, the product itself was of interest as it differs solely from the physiologically important hydrocortisone by the configuration of the C-11 hydroxyl group.



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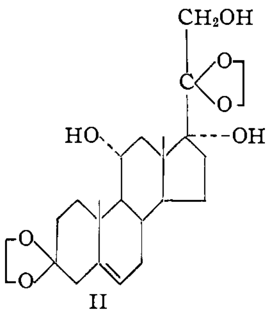

II

The microbiological preparation of 11-*epi*-hydrocortisone has been reported by Murray and Peterson,[2] and by Fried and co-workers.[3] Romo and co-workers[4] have announced the conversion of 11α-hydroxyprogesterone to 11-*epi*-hydrocortisone by incubation of the former with adrenal breis, as well as the chemical synthesis of 11-*epi*-hydrocortisone diacetate from Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate. A closely related synthesis of 11-*epi*-hydrocortisone diacetate has been described by Hershberg and co-workers.[5] It is to be noted that neither the Syntex nor Schering groups have prepared chemically the free steroid, 11-*epi*-hydrocortisone.

In view of the need for a more facile preparation of 11-*epi*-hydrocortisone, and, in general, of 11α-hydroxy-Δ^4-3-ketosteroids, this Laboratory has undertaken a study of the reduction of 11-ketosteroids. While this work was in progress there appeared two publications[5,6] which have an important bearing on this problem. It was shown that reduction of an 11-keto group with sodium and propanol gave in good to excellent yields the corresponding 11α-hydroxy compound. In light of this work, we wish to record that this conversion has been accomplished independently in this Laboratory by use of lithium in liquid ammonia in the presence of alcohol.[7] Under these conditions, the diethylene ketal (I) of cortisone was transformed in 82% yield to the practically pure 11α-hydroxy compound (II). Compound II was identical with the material obtained in the lithium aluminum hydride reduction. Acid hydrolysis gave in 60% yield pure 11-*epi*-hydrocortisone.

This procedure, which involves protection of the reactive keto-groups as ethylene ketals followed by lithium–liquid ammonia–alcohol reduction of the 11-keto group, is apparently general, and has been applied successfully to adrenosterone. The latter was converted accordingly into Δ^4-androstene-11α-ol-3,17-dione.

Experimental[8]

Diethylene Ketal of 11-*epi*-Hydrocortisone (Δ^5-Pregnene-11α,17α,21-triol-3,20-dione-3,20-diethylene Ketal) (II).—

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(1) Paper III, R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, in press.

(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952).

(3) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(4) J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chemistry and Industry*, 783 (1952).

(5) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **74**, 4470 (1952).

(6) H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(7) This reduction procedure was suggested by the work of F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2696 (1952).

(8) All m.ps. are uncorrected and were determined with uncalibrated Anschütz thermometers. All optical rotations are for 2 ml. of solution in the stated solvent and were determined in a 1-dm. semimicro tube.

A stirred solution of I (0.85 g.) in 35 ml. of dioxane, 10 ml. of ether, 6 ml. of absolute alcohol and 150 ml. of liquid ammonia was treated portionwise with 1 g. of lithium metal. The mixture was stirred at room temperature for two hours when the excess ammonia had spontaneously evaporated. Extraction with ethyl acetate and evaporation *in vacuo* afforded about 900 mg. of white powder, m.p. 288–291°. The crude product was treated with 40 ml. of acetone, cooled and practically pure II was collected: wt. 700 mg., m.p. 297–298°, yield, 82%.

A 70-mg. sample recrystallized from methanol–acetone afforded 50 mg. of pure II, m.p. 300–301°. Admixture m.p. determination with an authentic sample[1] showed no depression: $[\alpha]^{26}\text{D}$ −36° (19.3 mg., pyridine, αD −0.35°).

11-*epi*-Hydrocortisone.—Compound II (0.4 g., m.p. 297–298°) in 30 ml. of methanol and 4 ml. of 8% (v./v.) sulfuric acid was hydrolyzed in the manner previously described.[1] This gave 193 mg. (60% yield) of pure 11-*epi*-hydrocortisone (recrystallized from acetone–petroleum ether, b.p. 64–66°), m.p. 214–216°, $[\alpha]^{25}\text{D}$ +116° (20.1 mg., absolute alcohol, αD +1.16°), $\lambda_{\max}^{\text{abs. alc.}}$ 241–242 mμ, ε 14,800. Admixture m.p. determination, and absorption analysis (infrared, and sulfuric acid chromogen spectra) showed identity with an authentic sample.[1]

Diethylene Ketal of Adrenosterone (Δ^5-Androstene-3,11,-17-trione-3,17-diethylene Ketal).[9] A.—Adrenosterone[10] [$\lambda_{\max}^{\text{nujol}}$ 1730 cm.$^{-1}$ (17-keto), 1695 cm.$^{-1}$ (11-keto), 1660 cm.$^{-1}$ (3-keto), 1600 cm.$^{-1}$ (Δ^4), 1258 cm.$^{-1}$ (weak absorption), no hydroxyl absorption][11] (0.3 g.) in 25 ml. of benzene was treated with 2.2 ml. of ethylene glycol and 9 mg. of *p*-toluenesulfonic acid monohydrate in the manner previously described[12] (reflux, 5.5 hours). The crude product was recrystallized from ether, and ether–petroleum ether (64–66°); wt. 0.12 g., m.p. 184.5–185.5°, $\lambda_{\max}^{\text{abs. alc.}}$ none; $\lambda_{\max}^{\text{nujol}}$ 1695 cm.$^{-1}$ (11-keto), 1262 cm.$^{-1}$ (weak absorption), no hydroxyl absorption; $[\alpha]^{29}\text{D}$ −41° (13.5 mg., chloroform, αD −0.28°).

Anal.[13] Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.84; H, 8.28.

B.—In another run with 1 g. of adrenosterone, 50 ml. of benzene, 8 ml. of ethylene glycol and 30 mg. of *p*-toluenesulfonic acid monohydrate (reflux, 6 hours), there was obtained 0.93 g. (72%), m.p. 182–184°.

Δ^5-Androstene-11α-ol-3,17-dione-3,17-di-ethylene Ketal.—The diketal of adrenosterone (0.68 g.) in 25 ml. of dioxane, 5 ml. of absolute alcohol and 140 ml. of liquid ammonia was treated with about 1 g. of lithium in the manner described above. Evaporation *in vacuo* of the ethyl acetate extract afforded 0.67 g. of a white powder, m.p. 196–210°. One recrystallization from acetone–petroleum ether (64–66°) gave 0.4 g. (58%), m.p. 217–220°. An aliquot (150 mg.) on further recrystallization gave 120 mg., m.p. 219.5–221°, $\lambda_{\max}^{\text{nujol}}$ 3450 cm.$^{-1}$ (11-hydroxy), 1259 cm.$^{-1}$ (weak absorption), no carbonyl absorption; $[\alpha]^{26}\text{D}$ −71° (25.5 mg., chloroform, αD −0.90°).

Anal. Calcd. for $C_{23}H_{34}O_5$ (390.50): C, 70.74; H, 8.78. Found: C, 70.98; H, 8.72.

Δ^5-Androstene-11α-ol-3,17-dione-11-acetate-3,17-di-ethylene Ketal.—The free steroid (100 mg.) in pyridine was acetylated at room temperature, and afforded 53 mg. of acetate (recrystallized from acetone–methanol), m.p. 199–200°, $\lambda_{\max}^{\text{nujol}}$ 1718 cm.$^{-1}$ (11-acetoxy), 1252 cm.$^{-1}$ (strong absorption, 11-acetoxy), no hydroxyl absorption; $[\alpha]^{25}\text{D}$ −92° (12.2 mg., chloroform, αD −0.56°).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.27; H, 8.25.

Δ^4-Androstene-11α-ol-3,17-dione.—A solution of the 11α-ol-3,17-diketal (200 mg., m.p. 217–220°) in 5 ml. of glacial acetic acid was heated on the steam-bath, and was treated with 2 ml. of water. The heating was continued for 25 minutes when additional water was added. The mixture was cooled and neutralized with sodium bicarbonate solution. The crystals were collected and washed with water, 100 mg. (60%), m.p. 224–227°. Two recrystallizations from acetone–petroleum ether (64–66°) gave 65 mg., m.p. 227.5–229°, $\lambda_{\max}^{\text{abs. alc.}}$ 241 mμ, ε 14,800; $\lambda_{\max}^{\text{nujol}}$ 3390 cm.$^{-1}$ (11-hydroxy), 1735 cm.$^{-1}$ (17-keto), 1645 cm.$^{-1}$ (3-keto), 1606 cm.$^{-1}$ (Δ^4); $[\alpha]^{25}\text{D}$ +165° (11 mg., chloroform, αD +0.91°), $[\alpha]^{25}\text{D}$ +146° (11.5 mg., absolute alcohol, αD +0.84°); literature[2]: m.p. 226–227°, $[\alpha]^{24}\text{D}$ +162° (chloroform).

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The High Field Conductance of Aqueous Solutions of Glycine at 25°[1]

BY DANIEL BERG AND ANDREW PATTERSON, JR.

RECEIVED OCTOBER 4, 1952

The high field conductance of aqueous solutions of glycine, in the order of 0.1 to 1.6 molar, has been measured relative to hydrochloric acid at 25°. Two previous determinations of the high field conductance of glycine solutions have been reported.[2,3] These two sets of determinations are not in agreement with the observations reported herewith, and accordingly some discussion and explanation are in order. In this connection our results for a group of preliminary experiments on three separate samples of glycine are informative; these results are also presented briefly.

Experimental and Results

Both low and high field conductance measurements were carried out according to the procedure of Gledhill and Patterson[4] using a differential pulse transformer bridge circuit. The temperature control was to within 0.015°; the temperature of 25° was established with reference to a recently calibrated platinum resistance thermometer.

One conductance measurement was made on an unpurified stock sample of glycine. In this case the solid amino acid was added to the conductance cell with a spatula until a desired resistance was obtained. The concentration was determined to be approximately 0.12 molar by evaporating the water from a weighed portion of the solution and weighing the residue. The results obtained are shown as the lowest curve in Fig. 1. A second determination was made on a three-times recrystallized portion of the material originally employed. The glycine was recrystallized from conductivity water, filtered under suction, washed, and finally dried in a desiccator over sulfuric acid. The amount of material obtained was sufficient only to bring the cell resistance to approximately 3600 ohms, which was higher than desired. The concentration was approximately 0.6 molar. The results of the high field conductance determination on this solution are shown as the highest curve in Fig. 1. Because of the striking difference between these results and those obtained on the unpurified sample, approximately 10^{-5} mole of ammonium chloride was added to the liter of glycine solution in the conductance cell to bring the resistance to 1200.0 ohms and the high field conductance redetermined on the mixed electrolyte solution. The results are shown as curve C of Fig. 1. Finally, determinations were made on a once-recrystallized sample of Eastman ammonia-free glycine. The results of two determinations on the same solution are shown as curve B of Fig. 1. The concentration of the glycine solution was 1.644 molal, determined from the carefully weighed quantities of glycine and conductivity water used in preparation of the solution. In all cases a hydrochloric acid solution of appropriate resistance was used as reference solution.

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(9) This preparation was carried out by Robert Lenhard.

(10) T. Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

(11) We wish to thank William Fulmor for the infrared spectrograms.

(12) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(13) We wish to thank Louis M. Brancone, Samuel S. Modes and Edward B. Ruffing, Jr., for the microanalytical data.

(1) Contribution No. 1101 from the Department of Chemistry Yale University.

(2) M. Wien, *Phys. Z.*, **32**, 545 (1931).

(3) O. Blüh and P. Terentiuk, *J. Chem. Phys.*, **18**, 1664 (1950).

(4) J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, **56**, 999 (1952); also *Rev. Sci. Instr.*, **20**, 960 (1949).

Discussion

No claim is made for the accuracy of curves C or D; they indicate the importance of removal of other electrolytes from the glycine solution. Curve B conforms sufficiently to a straight line to convince one that a solution of carefully purified glycine behaves as do solutions of weak electrolytes. In comparison with acetic acid the results for glycine are, at 50 kv./cm., 1.8%; for acetic acid at the same field, 1.75%; at 100 kv./cm., glycine, 3.92%; acetic acid, 4.86%. The slope of the acetic acid curve is greater and the negative intercept of the curve is greater; glycine appears accordingly somewhat stronger than acetic acid. However, the concentration of the acetic acid, the data for which are taken from Bailey and Patterson,[5] was 7.405×10^{-4} molar, while the concentration of the glycine solution was 1.644 molar. It is obviously unwarranted to compare the high field conductance of glycine and acetic acid in terms of so simple a concept as relative strongness or weakness. Glycine has been shown to be principally in the form of zwitterions in solution: $NH_3^+CH_2COO^-$. The comparatively very high concentration of glycine required to provide an appreciable electrolytic conductance is in accord with this fact. This being so, the necessity of using very carefully purified materials is apparent. The *p*H of the solution used for curve B was measured as 5.9; the isoelectric *p*H of glycine is 5.96. The acid and base ionization constants are given as[6] $K_a = 4.47 \times 10^{-3}$; $K_b = 6.04 \times 10^{-5}$ at 25°. We may therefore conclude that the ionic entities present in greater concentration and thus the equilibrium more likely to be affected by the high field are represented by the acid ionization

$$(NH_3CH_2COOH)^+ \rightleftarrows NH_3^+CH_2COO^- + H^+$$

while the basic ionization

$$(HONH_3CH_2COO)^- \rightleftarrows NH_3^+CH_2COO^- + OH^-$$

is of lesser importance. With these assumptions, it is proper to conclude that, as with acetic acid,[5] the conductance is principally due to hydrogen ion and that one is dealing with a stronger acid, $K(0) = 4.47 \times 10^{-3}$, than acetic acid, $K(0) = 1.75 \times 10^{-5}$. It is thus natural that the slope of the high field conductance curve should be smaller than that of acetic acid.

Schiele's experimental data[7] for chloroacetic acid, $K(0) = 1.38 \times 10^{-3}$ at 25°, are drawn as curve E in Fig. 1 for comparison. It is not possible to compute a theoretical curve for glycine due to lack of necessary data. The comparison with Schiele's data is only approximate because the temperature of Schiele's measurement is not known, the $K(0)$'s do not correspond exactly, and glycine has both a K_a and a K_b, but the comparison does suggest a reasonable explanation for the magnitude of Wien effect observed with glycine. The small negative intercept of the extrapolated curve B indicates that some interionic attraction effects are present.

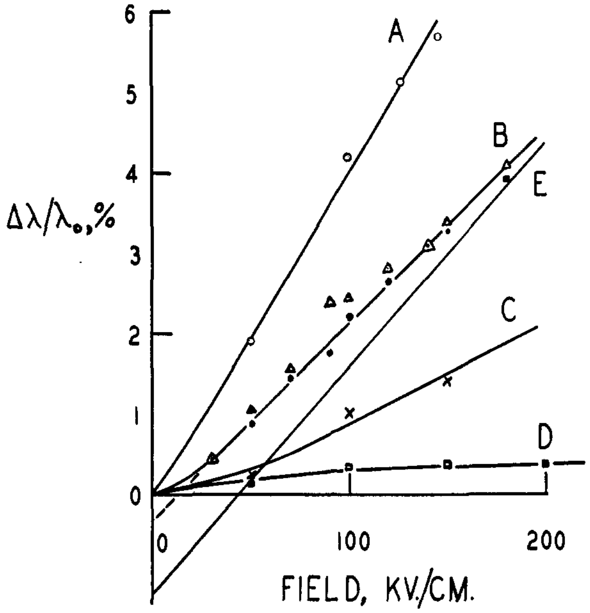

Fig. 1.—The high field conductance of aqueous solutions of glycine at 25°: A. carefully purified glycine, 0.6 molar; B. two determinations on a solution of carefully purified glycine. 1.644 molal; C, same solution as for curve A with approximately 10^{-5} mole of ammonium chloride added; D, unpurified stock sample of glycine, approximately 0.12 molar; E. Schiele's data (ref. 7) for chloroacetic acid.

It is also notable that curve A, for glycine at the smaller concentration 0.6 molar, compared to 1.6 molar for curve B, exhibits a larger Wien effect. In the more dilute solution a proportionately larger contribution might be expected from the weaker basic ionization equilibrium, so that the change of $K(X)$ with increasing field would be greater.

Our data do not agree with those of Wien[2] or of Blüh and Terentiuk.[3] Wien's results show a curve typical of a strong electrolyte and a Wien effect of about 5% at 100 kv./cm., while the concentration is reported as 5×10^{-5} molar. Since no data are given by Wien on the conductance cell constant or the source or preparation of his sample, it can only be assumed that the aminoacetic acid employed was highly contaminated by strong electrolytes. Blüh and Terentiuk report measurements at three values of field: at 60 kv./cm., 4.8%; at 80 kv./cm., 7.6 and 7.0%; and at 100 kv./cm., 10.0%; and for two concentrations, 64.0 g./l. and 38.1 g./l. (Our concentration for curve B was approximately 120 g./l.; for curve A, approximately 45 g./l.) These values of Wien effect are considerably larger than those which we report herewith.

Blüh and Terentiuk report a fractional high field conductance quotient of 4.2% for a solution containing 0.040 g. potassium chloride per liter, at 100 kv./cm. For such a solution the Onsager–Wilson equations[5] give a high field conductance quotient of 0.336% at 25°; we have found the Onsager–Wilson calculation entirely adequate to permit accurate computation of high field conductance for such a well known and simple valence type electrolyte as potassium chloride. The circuit diagram given by Blüh and Terentiuk does not appear to show any arrangement for reactance balancing, and accord-

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(5) F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4756 (1952).

(6) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2d ed., Reinhold Publishing Corp., New York, N. Y., 1950.

(7) J. Schiele, *Ann. Physik*, [5] **13**, 811 (1932).

ingly the results obtained for cell resistance would not reveal the true electrolytic resistance, but rather the cell impedance. If the usual parallel R–C circuit is assumed for a conductance cell, the apparent resistance equivalent of the impedance will be lower than the resistive component and the high field conductance quotients calculated from the data will be too large. Furthermore, should the capacitive component of the cell impedance change with field, additional difficulties of interpretation would result. This may be the explanation for the high values of Wien effect for potassium chloride reported in ref. 2, and for the disparity between our data and those of ref. 2 for glycine. It would require quite involved instrumentation to provide the successive pulse method of Blüh and Terentiuk with a means for reactive balancing at a 100 pulses/second repetition rate unless the rate of rise of the field were made quite slow.

We found no evidence in the series of measurements reported herewith of unusual or notable dielectric behavior of the glycine solutions with increasing field. As with the determinations on acetic acid,[5] it was found necessary to employ hydrochloric acid as reference electrolyte in order to avoid apparent bridge unbalance due to polarization occurring in different degree in the measurement and in the reference cells.

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The High Field Conductance of Lanthanum Ferricyanide at 25°[1]

BY DANIEL BERG AND ANDREW PATTERSON, JR.

RECEIVED NOVEMBER 14, 1952

The high field conductance of lanthanum ferricyanide is of interest because the compound is a 3–3 valence-type electrolyte. Conductance data at low fields are available for it,[2] and it thus is possible to test the Onsager–Wilson theory[3] as well as the correction thereto suggested by Bailey and Patterson.[4] Previous determinations on 2–2 valence-type electrolytes have been reported for magnesium sulfate,[5] zinc sulfate[6] and copper sulfate.[7] High field conductance measurements for lanthanum ferricyanide have not been previously reported. We have determined the high field conductance of aqueous solutions of lanthanum ferricyanide, approximately 10^{-4} molar, relative to potassium chloride at 25°.

Determinations were made on three solutions of lanthanum ferricyanide of slightly differing concentration. The procedure employed was identical with that of Gledhill and Patterson.[6] All measurements were made with four microsecond pulse duration. The lanthanum ferricyanide employed was a C.P. sample from the Delta Chemical Works, New York City; it was prepared from lanthanum nitrate and potassium ferricyanide and it is thus probable that there was some potassium nitrate present as contaminant. The sample was guaranteed to be better than 99% pure; we shall discuss the probable purity of the sample in terms of the conductance results obtained with it. The lanthanum ferricyanide was used in the form of a strong stock solution, approximately 0.013 molar; the solutions for conductance determinations were prepared by weight dilution with conductivity water in the conductance cells. The potassium chloride reference solutions were of such concentration as to give a suitable resistance in the comparison cell, and thus near 3×10^{-4} molar. The temperature was maintained at 25 ± 0.015° referred to a recently calibrated platinum resistance thermometer.

The results are presented in Fig. 1 as three curves, B, C and D, for solutions of concentrations 1.032×10^{-4} molar, 1.025×10^{-4} molar, and 1.023×10^{-4} molar, respectively, based upon the formula $La(Fe(CN)_6)\cdot 5H_2O$. Curve A is a portion of the data computed according to the procedure outlined in ref. 4; curve E is for the Onsager–Wilson theory.[3] It will be observed that at 200 kv./cm. the fractional high field conductance quotient has a value of some 20% compared with a value of 3.3% for magnesium sulfate and with a value of 0.41% for potassium chloride, all at equivalent concentrations. At the same field the Onsager–Wilson theory yields a value of 7.39%, and the calculation of Bailey and Patterson[4] a value of 36.3%; both values depart widely from the quantity experimentally observed, curve B. The experimental results bend over in the manner characteristic of strong electrolytes even though the fractional high field conductance quotient is quite large. Filled circles near curve B will be discussed below.

In previous work we have found that a small amount of electrolytic impurity in the presence of an electrolyte under study may profoundly alter the shape of the Wien effect curve and the magnitude of the Wien effect. Glycine was found[8] to be especially sensitive in this respect: only 10^{-5} mole of ammonium chloride in a 0.6 molar glycine solution was sufficient entirely to alter the nature of the results obtained. It is thus necessary to demonstrate the effects of possible impurities such as potassium nitrate on the high field conductance results.

If we assume that there was present in the lanthanum ferricyanide 1% of potassium nitrate, and if we further assume that the same results would obtain if the pure salts were placed in separate conductance cells rather than (as in the actual experiment) in the same conductance cell, and the two cells then operated in parallel, we may calculate as follows: For potassium nitrate the value of Λ^0 is 145 and the concentration is 10^{-6} molar; for the lanthanum ferricyanide Λ^0 is 168 and the concentration is 10^{-4} molar. The resistance of the potassium nitrate solution will thus be approximately 100 times that of the lanthanum ferricyanide. If the resistance of the lanthanum ferricyanide solution is 1010 ohms and that of the potassium nitrate 101,000 ohms, the parallel circuit will have a resistance of 1000 ohms. If the resistance of the lantha-

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[1] Contribution No. 1132 from the Department of Chemistry, Yale University.

[2] C. W. Davies and J. C. James, *Proc. Roy. Soc.* (*London*), **A195**, 116 (1948).

[3] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1950.

[4] F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4428 (1952).

[5] F. E. Bailey and A. Patterson, *ibid.*, **74**, 4428 (1952).

[6] J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, **56**, 999 (1952).

[7] D. Berg and A. Patterson, THIS JOURNAL, **74**, 4704 (1952).

[8] D. Berg and A. Patterson, *ibid.*, submitted for publication.

num ferricyanide cell decreases to 840 ohms as a result of the application of a 200 kv./cm. field, the fractional high field conductance quotient will be 20.2%. Under the same field the potassium nitrate cell will decrease in resistance to 100,600 ohms to yield a quotient of 0.4%. The parallel resistance of the two cells with field applied will be 833 ohms, and the computed fractional high field conductance quotient is then 20.0%. The resulting conductance measurement on the combined solution is thus in error by 0.2 in the term $\Delta\lambda/\lambda_0$ (%) at 200 kv./cm. If there is less potassium nitrate present, the error will be smaller. An error of 0.2 in $\Delta\lambda/\lambda_0$ (%) is almost ten times the reproducibility of results for repeated determinations on the same solution at the same field, but it is obviously only 1% of the quantity being measured. In view of the large Wien effect obtained experimentally, the shape of the Wien effect curve (Fig. 1), and the calculation, above, we are inclined to believe that the effect of electrolytic impurities such as potassium nitrate is in this case quite small; such would definitely not be the situation in an absolute conductance measurement, in contrast with the present measurements, which are relative only. We have checked these ideas by the addition of small amounts of potassium nitrate to the solutions of lanthanum ferricyanide; indeed, with potassium nitrate of 1.29×10^{-4} molar concentration and lanthanum ferricyanide of 0.648×10^{-4} molar concentration together, the high field conductance curve of the mixture lies two units above curve E at 200 kv./cm. The results reported herewith, curves B, C and D, are thus thought to be accurate to well within the factor of 0.1%, absolute, which has previously been claimed.[9]

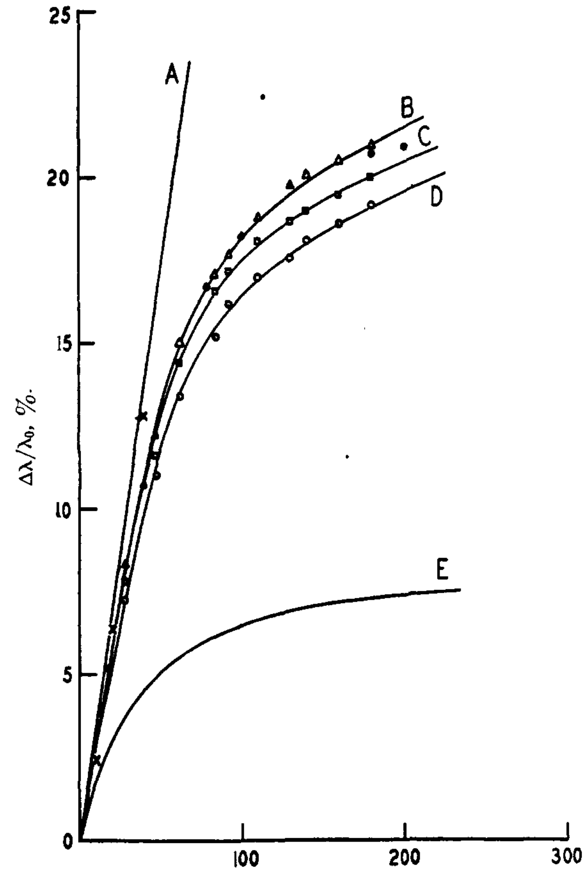

Fig. 1.—The high field conductance of aqueous solutions of lanthanum ferricyanide: A, (x) corrected Onsager–Wilson theory as in ref. 4; B, (Δ) 1.032×10^{-4} molar solution; C, (□) 1.025×10^{-4} molar solution; D, (O) 1.023×10^{-4} molar solution; E, Onsager–Wilson theory as in ref. 3; filled circles between curves B and C, corrected Onsager–Wilson theory using selected value of $K(0) = 3.50 \times 10^{-4}$.

TABLE I

CORRECTED ONSAGER–WILSON THEORY FOR THE HIGH FIELD CONDUCTANCE OF LANTHANUM FERRICYANIDE RELATIVE TO POTASSIUM CHLORIDE AT 25° USING SELECTED VALUE OF $K(0) = 3.702 \times 10^{-4}$

$LaFe(CN)_6$, 1.025×10^{-4} molar $\Lambda^0 = 168.9$ KCl, 3.0×10^{-4} molar $\Lambda^0 = 149.85$

Field, kv./cm.	$F(b)$	α	$\alpha\{\Lambda^0 - S\Lambda_x (\alpha c)^{1/2}\}$	$\frac{\Delta\lambda}{\lambda_0}$ corr., %	$\frac{\Delta\lambda}{\lambda_0}$ rel., %
0	1	0.8790	135.23	0.00	0.00
20	1.9559	.88435	139.64	3.26	3.16
40	3.4545	.9301	148.88	10.10	9.90
80	8.9549	.9708	157.16	16.21	15.91
100	13.6226	.9805	159.18	17.71	17.37
180	57.7882	.9953	162.56	20.21	19.81
200	79.5997	.9965	162.92	20.47	20.05

In similar determinations with magnesium, zinc and copper sulfates the agreement between the experimental results and the corrected theory was considerably better than obtained in the present case. With a 3–3 electrolyte the influence of the value of $K(0)$ chosen is particularly important. Referring to equation (8) of ref. 4, we observe that the value of α at zero field is necessarily smaller for the weaker 3–3 electrolyte, and the change of α with increasing field proportionately greater than for 2–2 electrolytes. Stated in another fashion, the weak electrolyte high field effect is much more important than the strong electrolyte high field effect for a 3–3 electrolyte. Since the value of the high field conductance quotient is a sensitive function of $K(0)$, we have utilized the experimental results of the present paper to compute a value of $K(0)$ which is concordant with the experimental results. Because the quantities α and $K(0)$ are interrelated, this computation required a certain amount of successive approximation. The values of $K(0)$, α, field and $\Delta\lambda/\lambda_0$ chosen or computed are given in Table I in the same form as Table I of ref. 4. Consistent values of $\alpha = 0.8790$ and $K(0) = 3.702 \times 10^{-4}$ were obtained; the expressions

$$\log \frac{\alpha^2 c}{3(1 - \alpha)} + \log \frac{y^2 \pm}{y_u} = \log K(0) \qquad (1)$$

where

$$\log \frac{y^2 \pm}{y_u} = -9 \left\{ \frac{\Gamma^{1/2}}{1 + \Gamma^{1/2}} - 0.20\,\Gamma \right\} \qquad (2)$$

with the terms as defined by Harned and Owen,[3] were used to relate α and $K(0)$. The value of $K(0)$ obtained by Davies and James was 1.82×10^{-4}. The filled circles lying between curves B and C of Fig. 1 are plotted from data computed in the same

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[9] F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4426 (1952).

way as Table I, but for $K(0) = 3.50 \times 10^{-4}$ and $c = 1.025 \times 10^{-4}$ molar. The data for the last column of Table I lie very close to curve C. Thus a difference of this order in $K(0)$ gives rise to a difference in $\Delta\lambda/\lambda_0$ (%) of one unit. This procedure therefore constitutes a sensitive method for estimation of $K(0)$.

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Exchange Reactions of Methane and Monodeuteromethane with Atomic Deuterium

BY D. W. COLLET AND G. M. HARRIS

RECEIVED NOVEMBER 8, 1952

The reaction of atomic deuterium, produced by the discharge-tube method, with methane has been investigated a number of times.[1] The reaction takes place at an appreciable rate only at elevated temperatures, as it appears to have both a relatively high activation energy and a relatively low steric factor.[2] As yet, no unequivocal choice of mechanism for the exchange has been possible. The suggestions are (a) hydrogen abstraction, $D + CH_4 = CH_3 + HD$, followed by exchange of the methyl radical prior to stabilization as a deuteromethane, and (b) an inversion process, $D + CH_4 = CH_3 + H$. Since CH_3 radicals are known to exchange rapidly with D atoms,[3] in excess of the latter mechanism (a) would lead to CD_4 as the major exchange product. With mechanism (b) operative, the major product would be CH_3D. In the present work, the distribution of product deuteromethanes from the $D + CH_4$ reaction has been determined by means of mass spectrometry. CD_4 was found to constitute about 80% of the exchange product, most of the remaining deuteromethane being CHD_3. Strong evidence is thus provided that mechanism (a) alone accounts for this exchange.

In an extension of this work, the analogous $D + CH_3D$ reaction was investigated with a view to determining the nature of possible isotope effects. In terms of mechanism (a), the rate-determining reactions to be considered are

$$D + CH_4 = CH_3 + HD \text{ (rate constant } = 4k_1)$$
$$D + CH_3D = CH_2D + HD \text{ (rate constant } = 3k_2)$$
$$D + CH_3D = CH_3 + D_2 \text{ (rate constant } = k_3)$$

k_2 and k_3 should differ in magnitude due to zero-point energy differences. Taking the values of the C–H and C–D stretching frequencies in CH_3D to be 3000 and 2200 cm.$^{-1}$,[4] one can readily estimate the rate constant ratio $k_3/k_2 = 0.40$ at 350°.[5] Whence, if k_1 and k_2 are assumed identical, the relative rates of exchange of CH_3D and CH_4 should be $(3k_2 + k_3)/4k_1 = 0.85$. In the present study, known mixtures of CH_3D and CH_4 were exchanged with atomic deuterium, and it was found that the CH_3D/CH_4 ratio did not change within the experimental error during 50% reaction. Since it is inconceivable that k_2 and k_3 be identical, it appears that k_2 must in fact be greater than k_1. Support for this hypothesis comes from the data on electron-impact bond-breakage probabilities for C–H in CH_4, C–H in CH_3D and C–D in CH_3D. A ratio of 1.00:1.21:0.46 is obtained if one averages the results of the several studies reported.[6] If the D-atom exchange rate constants bear the same type of relationship to one another, nearly identical rates of exchange for CH_4 and CH_3D are to be expected, since in this event $(3k_2 + k_3)/4k_1 = 1.02$.

Experimental

The exchanges were effected in a conventional Wood tube type of apparatus,[7] utilizing a water-jacketed discharge-tube and a 2.5 liter spherical reactor flask. The reactor was enclosed by an electrically-heated transite oven, and its temperature controlled manually, temperature readings being taken on three strategically placed thermocouples on the walls of the bulb. Atom concentrations, which ranged between 10 and 20% in the various experiments, were estimated by means of a Wrede–Harteck gage. The glass surface of the reactor was "poisoned" toward hydrogen atom recombination by a coating of pyrophosphoric acid, which proved quite effective even at the elevated temperatures of the experiments. The methane reactant was introduced into the center of the reaction vessel at a rate of about 1 cc. per minute at N.T.P. At the low pressure within the reactor (0.5 mm.) rapid diffusional mixing with the excess of partially dissociated deuterium took place (rate of deuterium flow was 65 cc. per minute at N.T.P.). On leaving the reactor, the methane products and a small amount of deuterium were retained in a silica gel trap maintained at liquid air temperature. At the completion of the run, usually of 10 to 15 minutes duration, the methanes were separated from the adsorbed deuterium by repeated distillation between two alternately chilled silica gel traps. The methanes were then completely desorbed by warming to −80° and samples taken for mass spectrometric assay.

Pure methane was prepared by the hydrolysis of methylmagnesium iodide in an atmosphere of hydrogen. The Grignard was prepared as a paste in dioxane, and aqueous dioxane added as hydrolyzing reagent. The gas was purified by passage through traps at Dry Ice and liquid air temperatures, and finally condensed into a pumped-down liquid-oxygen-cooled trap at −215°. Monodeuteromethane of high purity was similarly prepared, using rigorously dehydrated solvent and 99.97% heavy water. The methane/deuteromethane mixtures for use in the isotope effect experiments were made up manometrically. Deuterium was produced by the electrolysis of 99.97% heavy water containing a little NaOD. Small samples of CH_2D_2 and CHD_3 were prepared for mass spectrometer calibration purposes by the action of aluminum/mercury couple on CH_2I_2 and $CHBr_3$, respectively, in the presence of 99.97% heavy water.

The mass spectrometric analyses were performed on a Consolidated Engineering Corporation mass spectrometer. Calibration spectra of CH_4, CH_3D, CH_2D_2 and CHD_3 were obtained from samples of these gases as prepared above, while that of CD_4 was calculated from the spectrum of CH_4, to which it is closely enough analogous for our purpose.[6b,c] The parent peak sensitivities of the various methanes were assumed identical in making the composition computations. The percentages quoted for CH_4, CH_3D, CHD_3 and CD_4 are probably accurate to within one unit, but there is more uncertainty concerning the CH_2D_2 due to the large overlap of

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[1] E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, N. Y., 1946, pp. 253–259.

[2] T. G. Majury and E. W. R. Steacie, *Disc. Far. Soc.*, "The Reactivity of Free Radicals," Toronto, Sept. 1952, Paper No. 4.

[3] N. Trenner, K. Morikawa and H. S. Taylor, *J. Chem. Phys.*, **5**, 203 (1937).

[4] G. Herzberg, "Infrared and Raman Spectra," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 306.

[5] H. Eyring and F. W. Cagle, Jr., *J. Phys. Chem.*, **56**, 889 (1952).

[6] (a) M. W. Evans, N. Bauer and J. Y. Beach, *J. Chem. Phys.*, **14**, 701 (1946); (b) V. H. Dibeler and F. L. Mohler, *J. Research Natl. Bur. Standards* **45**, 441 (1950); (c) D. O. Schissler, S. O. Thompson and J. Turkevich, *Disc. Far. Soc.*, **10**, 46 (1951).

[7] Reference (1), p. 33–36.

peaks and the fact that it was present in only small amount if at all. There could have been as much as 3% of this constituent without a clear indication of its presence.

The results obtained are tabulated below. The evidence for near-complete exchange is clear in every instance. Experiments 7 and 8 show unmistakably that there is no appreciable difference in the rates of CH_4 and CH_3D exchange.

Expt. no.	2	3	4	5	6	7	8
Temp., °C.	360	340	342	365	370	350	350
Reactant methanes, %							
CH_4	100	100	100	0	0	50	33
CH_3D	0	0	0	100	100	50	67
Product methanes, %							
CH_4	39	50	52	0	0	26	16
CH_3D	3	3	2	53	53	25	34
CH_2D_2	0	0	0	0	0	0	0
CHD_3	8	6	4	8	7	11	10
CD_4	50	41	42	39	40	38	40

Acknowledgment.—The authors are grateful to Dr. J. D. Morrison of the C.S.I.R.O. Division of Industrial Chemistry, Melbourne, for his very great assistance in the obtaining and interpretation of the mass spectrograms.

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A Kinetic Study of the Perkin Condensation[1]

BY ROBERT E. BUCKLES AND KEITH G. BREMER

RECEIVED NOVEMBER 7, 1952

Base-catalyzed, aldol-type condensations of carbonyl compounds with weak secondary acids capable of losing a proton have been studied to some extent from the standpoint of kinetics and mechanisms.[2] No kinetic studies have been made on the Perkin condensation, but its mechanism has been formulated as an aldol-type condensation of an acid anhydride with an aromatic aldehyde.[2a]

The present investigation is concerned with the kinetics of the base-catalyzed condensation of benzaldehyde with phenylacetic acid in acetic anhydride. This particular condensation is of interest as a starting point in the study of the effect of substituents on the benzene ring of both the benzaldehyde and the phenylacetic acid.

Experimental

Reagents.—Commercial benzaldehyde was washed with 10% aqueous sodium carbonate and then with water. It was dried over magnesium sulfate and distilled at reduced pressure (below 30 mm.) in the presence of a little hydroquinone. The acetic anhydride was distilled at 745 mm., and the fraction boiling 137–139° was used. Both of these reagents were purified in small quantities and were used as soon as possible.

The anhydrous amines were obtained from Sharples Chemicals, Inc. The phenylacetic acid was a recrystallized commercial preparation of m.p. 76–77°.

Product Isolation.—The condensation of 54.6 g. of phenylacetic acid and 42.4 g. of benzaldehyde in 80 ml. of acetic anhydride containing 40 ml. of triethylamine was carried out as described before.[3] From the reaction mixture was isolated 60–67 g. (67–75%) of crude α-phenylcinnamic acid of m.p. around 156°. From this crude product 48–52 g. (54–58%) of product of m.p. 172–173° could be obtained by crystallization from 50% ethyl alcohol.

In a similar experiment carried out at room temperature for six days a 63% yield of crude product was obtained.

Kinetic Measurements.—The reactions were carried out in an all-glass apparatus consisting of a 500-ml. three-necked flask fitted with a long air condenser, protected from atmospheric water vapor, and a True-Bore glass stirrer. The reaction flask was immersed in a thermostatically controlled oil-bath whose heating element was contained in the wall of the bath. The temperature was kept constant to within 0.1° at the temperatures used. Varying amounts of phenylacetic acid in 150 ml. of acetic anhydride were added to the reaction flask and allowed to remain in the bath overnight. The benzaldehyde and the amine catalyst were then added with stirring. An initial 5-ml. sample was withdrawn into a pipet fitted with a hypodermic syringe as soon as the mixture was homogeneous. Further samples were taken at regular intervals of time thereafter. The analysis for benzaldehyde was carried out by a modification of the procedure described for the determination of carbonyl compounds in the presence of carboxylic acids.[4] A 5-ml. sample was added to 100 ml. of 90% aqueous methanol and the mixture was allowed to stand for 15 minutes so that the anhydride would be destroyed. The *p*H of the solution was then adjusted to 2.5 with 0.5 *N* aqueous hydrochloric acid and 25 ml. of the 0.5 *N* hydroxylamine hydrochloride in 80% ethyl alcohol (*p*H 2.5) was then added. After a reaction period of 15 minutes the hydrochloric acid formed was titrated with 0.463 *N* carbonate-free sodium hydroxide in 80% methanol to an end-point of *p*H 2.5. The results of the titration of the initial samples coupled with the initial mole ratios of the reagents added were used to calculate the initial concentrations of the runs. Satisfactory agreement within experimental error was obtained in a number of duplicate determinations. The runs with variations in concentrations, catalyst and temperature are summarized in Table I.

TABLE I

SUMMARY OF BASE CATALYZED CONDENSATIONS OF PHENYLACETIC ACID WITH BENZALDEHYDE IN ACETIC ANHYDRIDE AT 100°

Run	Concentrations of reagents, *M* PhCHO	$PhCH_2COOH$	Et_3N	$k \times 10^5$
1	1.058	1.058	0.000	. . .
2	1.002	1.002	.577	7.6
3	0.972	1.944	.560	6.2
4	1.889	0.964	.550	5.7
5	1.032	1.032	.297	7.5
6	1.007	1.007	.580[a]	6.9
7	0.978	0.978	.564[b]	5.9
8	1.076	1.076	.620[c]	5.1
9	1.198	1.198[d]	.690	0.18
10	1.261	0.000	.000	. . .
11	1.256	0.000	.723	0.15
12[e]	1.060	1.060	.611	1.04
13[f]	1.001	1.001	.577	6.3
14[g]	1.014	1.014	.584	10.2

[a] Tri-*n*-propylamine was used as a catalyst. [b] Tri-*n*-butylamine was used as a catalyst. [c] Potassium acetate was used as a catalyst. [d] Acetic acid was added in place of phenylacetic acid. [e] The reaction was carried out at 26°. [f] The reaction was carried out at 80°. [g] The reaction was carried out at 120°.

Results and Discussion

The various runs carried out and their results are summarized in Table I. Typical titration data for

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[1] From the Ph.D. thesis of Keith G. Bremer. Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September, 1952.

[2] (a) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 9. (b) J. D. Gettler and L. P. Hammett, THIS JOURNAL, **65**, 1824 (1943). (c) E. F. Pratt and E. Werble, *ibid.*, **72**, 4638 (1950). (d) T. I. Crowell and F. A. Ramirez, *ibid.*, **73**, 2268 (1951).

[3] R. E. Buckles, M. P. Bellis and W. D. Coder, Jr., *ibid.*, **73**, 4972 (1951).

[4] D. M. Smith and J. Mitchell, Jr., *Anal. Chem.*, **22**, 750 (1950).

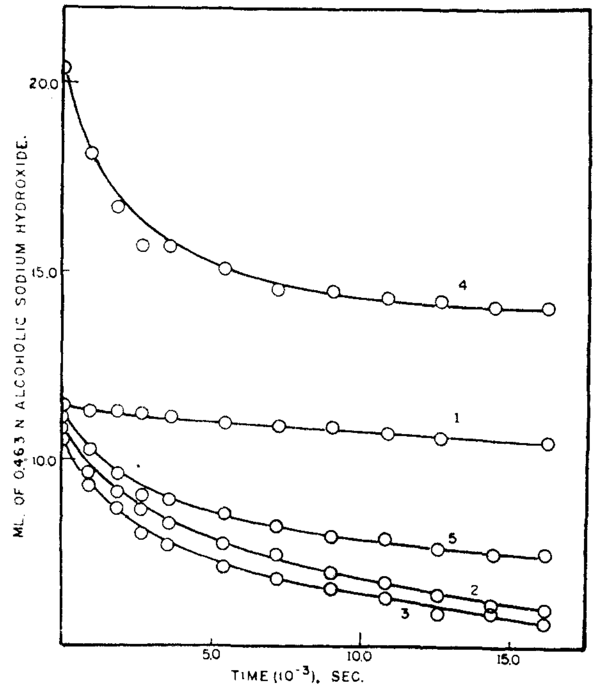


Fig. 1.—Representative titration curves for some of the runs listed in Table I.

several runs are shown graphically in Fig. 1. The slow disappearance of benzaldehyde presumably caused by autoxidation is illustrated in run 1 in which added catalyst was absent. A similar result was obtained when both catalyst and phenylacetic acid were absent (run 10). Of more consequence as a competing reaction was the condensation of benzaldehyde with acetic anhydride as shown in runs 9 and 11. This was a slower reaction than the apparent condensation of benzaldehyde with phenylacetic acid as shown by the kinetic results as well as by the fact that α-phenylcinnamic acid was isolated in a crude yield of 75% when the latter condensation was carried out in the presence of an excess of acetic anhydride. As a first approximation in the determination of specific rate constants for the apparent condensation of benzaldehyde with phenylacetic acid, these competing reactions of benzaldehyde were ignored.

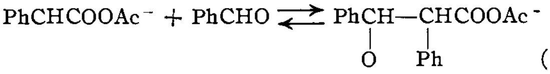
The rate law found to be most consistent with changes in the rate of reaction arising from changes in concentrations of the various reactants as well as from changes in the identity of the catalyst is given in equation (1). This equation can be derived from a mechanism such as that outlined in equations (2) through (7) if it be assumed that equation (5) represents the rate-determining step. Such a mechanism is consistent with results for aldol-type condensations.[2] The steps preceding (5) are considered to be essentially at equilibrium. It would be expected, however, that step (2) would be fairly complete to the right in the presence of the large excess of acetic anhydride, that step (3) would also be far in favor of the forward reaction as shown by a consideration of the relative acid and base strengths of acetic acid and the trialkylamines, and that step (4) would be far in favor of the reverse reaction. Thus, it can be assumed that the initial concentration of phenylacetic acid is equal to that of the mixed anhydride of phenylacetic and acetic acids, and also to the initial concentration of acetic acid. When the initial concentration of the amine is equal to or less than that of the phenylacetic acid plus any acetic acid (from step (7)), the concentration of acetate ion will be equal to the initial concentration of the amine.

$$\frac{dx}{dt} = \frac{k(\mathrm{PhCHO})(\mathrm{PhCH_2COOH})(\mathrm{AcO^-})}{(\mathrm{AcOH})} \qquad (1)$$

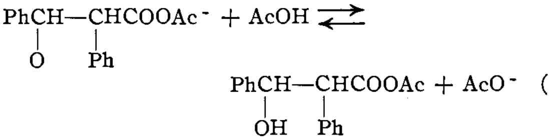
$$\mathrm{PhCH_2COOH + Ac_2O \rightleftharpoons PhCH_2COOAc + AcOH} \qquad (2)$$

$$\mathrm{R_3N + AcOH \rightleftharpoons R_3NH^+ + AcO^-} \qquad (3)$$

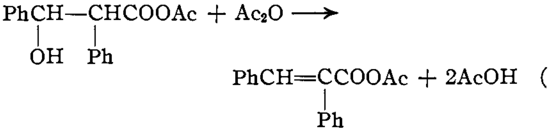
$$\mathrm{PhCH_2COOAc + AcO^- \rightleftharpoons PhCHCOOAc^-} \qquad (4)$$



$$\mathrm{PhCHCOOAc^- + PhCHO \rightleftharpoons \underset{O}{PhCH}-\underset{Ph}{CHCOOAc}^-} \qquad (5)$$



$$\mathrm{\underset{O}{PhCH}-\underset{Ph}{CHCOOAc}^- + AcOH \rightleftharpoons \underset{OH}{PhCH}-\underset{Ph}{CHCOOAc} + AcO^-} \qquad (6)$$



$$\mathrm{\underset{OH}{PhCH}-\underset{Ph}{CHCOOAc} + Ac_2O \longrightarrow PhCH{=}\underset{Ph}{CCOOAc} + 2AcOH} \qquad (7)$$

Steps analogous to (4), (5), (6) and (7) would be expected for the condensation of benzaldehyde with acetic anhydride. If this competing reaction is considered, the rate law is equation (8) where k' is the specific rate constant of the reaction with acetic anhydride.

$$\frac{dx}{dt} = \frac{k(\mathrm{PhCHO})(\mathrm{AcO^-})}{(\mathrm{HOAc})}\left[(\mathrm{PhCH_2COOH}) + \frac{k'}{k}(\mathrm{Ac_2O})\right] \qquad (8)$$

A first approximation of the value of k, the specific rate constant of the apparent condensation of benzaldehyde with phenylacetic acid was obtained by the use of equation (1). The approximate value of k as well as that of k', which was obtained similarly, was used in a second approximation by means of equation (8). The approximate values obtained are given in Table I. The average value of the specific rate constant at 100° was $(6.4 \pm 0.9) \times 10^{-5}$ liter per mole per second ($\pm 0.9 \times 10^{-5}$ determines the 95% confidence limits of the average). Considering the assumptions made and the difficulties encountered in following the reaction, the observed standard deviation of 8–14% for individual specific rate constants is not believed to be excessive. The effect of varying the concentrations of the reagents and the identity of the catalyst on the rate certainly lends support to the type of mechanism proposed. The reaction exhibits specific acetate ion catalysis when it is carried out in a large excess of acetic anhydride as a medium. Wide variations in yield reported[5] with different catalysts for this type of condensation would not be caused by differences in the initial rate of condensation, but by differences in side reactions,

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(5) M. Bakunin and D. Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935); R. E. Buckles and E. A. Hausman, This Journal, **70**, 415 (1948).

product decomposition, and other factors affecting the isolation of a product.

Variation of the specific rate constant with temperature is also shown in Table I (runs 13, 14 and 15). The reaction has a low temperature coefficient which is not particularly surprising for an aldol-type condensation.[2b]

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The Isolation of the Toxic Principles of Mamey

BY M. P. MORRIS AND C. PAGÁN

RECEIVED AUGUST 1, 1952

The insecticidal properties of the various parts of the mamey tree (*Mammea americana* L.) have been recognized for many years.[1] Although the seeds from the fruit of this tree have been the subject of numerous investigations,[2] the isolation of the toxic compounds in pure form has not been previously reported.

Outlined below is a procedure which led to the isolation of one pure, toxic, crystalline compound and to one toxic amorphous solid. These two substances were highly toxic to several species of insects and accounted for 81% of the toxicity of mamey extract. Their powerful action as fish poisons facilitated their isolation since this permitted the use of guppies as the bioassay test animal.

Experimental

Seeds of mature fruit were sectioned, dried at 45° in a forced-draft oven for 24 hours, ground to 80 mesh, and extracted for 8 hours with petroleum ether in a soxhlet type extractor. A light-red, sticky, semi-solid mass, representing 5% of the dried powder, was obtained after evaporation of the solvent. Heating under high vacuum for 2 hours at 100° was required for the removal of the last traces of solvent. Other non-polar solvents served as well as petroleum ether for this extraction. This semi-solid mass was dissolved in the minimum amount of acetone and placed in an ice-bath for 24 hours. A non-toxic white, powdery solid, melting sharply at 78°, was obtained. The yield was 1.5% of the dried extract. The acetone in the filtrate was evaporated under reduced pressure and the residue dissolved in petroleum ether to give a 10% solution. Fifty ml. of this solution, equivalent to 5.0 g. of dried extract, was placed on a 75 × 150 mm. column prepared with silicic acid (Merck 200 mesh) and developed with a 1:10 mixture of ether and petroleum ether. After the initial band had separated into three distinct bands, the silicic acid was extruded, sectioned, and the three bands extracted with ether. The immobile band at the top of the column was not toxic and was discarded. The procedure was repeated five times and the corresponding extracts of the two mobile toxic bands were combined. This gave a preliminary separation.

The ether solution of the leading toxic band was partially evaporated and the remaining ether gradually replaced with petroleum ether while boiling on a steam-bath. Cooling in an ice-bath for 24 hours produced 2.3 g. of well-formed, colorless crystals, representing several crystalline modifications. Numerous recrystallizations from ether–petroleum ether showed these crystals to be a mixture of compound A, m.p. 130–131° (2.1 g.), and several other crystalline compounds which have not yet been obtained in pure form. Compound A showed approximately the same LD_{50} as the original extract, *i.e.*, 1.5 p.p.m., and thus accounted for 7% of the toxicity of the original extract. The mother liquors when combined and partially evaporated yielded 0.5 g. of light-yellow crystals, m.p. 70–90°. This mixture was resolved into three crystalline substances, melting at 82–84°, 101–102° and 114–115°. These last three substances appeared to be solvates, for they effervesced strongly at their melting points.

Compound A dissolved readily in dilute alkali to give a yellow solution and gave positive phenolic tests. This compound added methylmagnesium bromide readily, but did not liberate methane in the Zerewitinoff apparatus. The ultraviolet absorption spectrum obtained with a Beckman model DU spectrophotometer, using 95% alcohol as the solvent, showed maxima at 244, 249. 255, 261 and 334 mμ.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.26; H. 7.33. Found: C, 71.15, 71.10; H, 7.62, 7.56.

The ether solution of the middle toxic band was evaporated and a light-red oil was obtained which was extracted several times with petroleum ether. The tacky residue that remained was taken up in a 1:10 ether–petroleum ether mixture and rechromatographed three times on a silicic acid column as described above. This led to the isolation of 3.1 g. of a highly toxic material. The LD_{50} of this golden-yellow amorphous substance which softened at 170–175°, was 0.25 p.p.m. by the guppy bioassay method[3] and accounted for 74% of the toxicity of the original extract. This LD_{50} of 0.25 p.p.m. indicated that this substance was approximately 20% as toxic as rotenone under the same conditions. The molecular structures of the toxic compounds described above are now being investigated by Professor J. L. E. Erickson, Louisiana State University. A report of this work will be submitted from his laboratory to THIS JOURNAL at a later date.

During the past year this Laboratory received several requests for samples of these pure toxic compounds, indicating a widespread interest in these potential insecticides. A recent press release[4] from the University of Puerto Rico stated that mamey extract contained "antibiotic substances which were active *in vitro* against one or more bacteria."

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(1) D. de Grosourdy, "El Médico Botánico Criollo," Vol. II(2), Paris, (1864), p. 511.

(2) M. A. Jones and H. K. Plank, THIS JOURNAL, **67**, 2262 (1945); H. K. Plank, *J. Econ. Entomol.*, **37** (6), 737 (1944), and refs. cited.

(3) C. Pagán, *ibid.*, **41** (6), 942 (1948).

(4) "Información Oficial," Núm. **19**, Oct. 4, 1951, Universidad de Puerto Rico.

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MAYAGUEZ, PUERTO RICO

An Investigation of the Hammick Reaction

BY NELSON H. CANTWELL AND ELLIS V. BROWN

RECEIVED NOVEMBER 13, 1952

In an attempt to elucidate the nature of the Hammick reaction[1,2] with a view to extending it, we varied the character of the carbonyl reactant by introducing substituents into its nucleus.

The various carbonyl compounds which were successfully coupled with picolinic acid upon decarboxylation are listed in Table I. In initial investigations various solvents such as dibromobenzene, nitrotoluene, bromoanisole, xylene and *p*-cymene, equivalent in amount to the aldehyde used were added to the reaction mixture to determine what effect they might have on the yield. This proved to be very practical for the yield of carbinol was increased in every case. The best yields were ob-

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(1) D. Ll. Hammick and P. Dyson, *J. Chem. Soc.*, 1724 (1937); 809 (1939).

(2) D. Ll. Hammick and B. R. Brown, *ibid.*, 173 (1949); 659 (1949).

TABLE I

HAMMICK REACTIONS WITH PICOLINIC ACID[a] AND VARIOUS CARBONYL COMPOUNDS

Carbonyl compound	Product	Yield Grams	Yield %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Benzaldehyde	Phenylpyridylcarbinol[d]	1.3	17[b]	78	...	...	...	..
		4.1	54[c]					
Benzophenone	Pyridyldiphenylcarbinol[d]	2.1	21[b]	105	...	...	..	.
		4.8	48[c]					
Acetophenone	Phenylpyridylmethylcarbinol[d]	1.9	23[b]	152 (745 mm.)[e]	...	...	..	..
		4.2	50[c]					
p-Methoxybenzaldehyde	*p*-Methoxyphenylpyridylcarbinol	2.3	26[b]	131				
		5.1	59[c]					
m-Nitrobenzaldehyde	*m*-Nitrophenyl pyridyl ketone	1.5	15[b]					
		4.7	48[c]	118	63.22	63.50	3.53	3.32
m-Nitroacetophenone	*m*-Nitrophenylpyridylmethylcarbinol	2.0	20[d]	130	63.91	64.12	4.91	4.86
		4.1	42[c]					
p-Chlorobenzaldehyde	*p*-Chlorophenylpyridylcarbinol	2.0	22[c]	83	65.96	66.32	4.51	4.43
		5.2	58[a]					

[a] 5 g. of acid in 30 g. of carbonyl compound. [b] Refers to reaction without solvent. [c] Refers to reaction with solvent (*p*-cymene). [d] Reference 1 and 2. [e] This is the boiling point.

TABLE II

Acid	Aldehyde	Temp., °C.	Result
Pyrimidine-4-carboxylic	Anisaldehyde	245	Neg.
Thiazole-2-carboxylic	Anisaldehyde	90	Neg.
	Benzaldehyde	90	Neg.
4,5-Dimethylthiazole-2-carboxylic	Anisaldehyde	93	Neg.
	Benzaldehyde	93	Neg.
4-Methylthiazole-5-carboxylic	Benzaldehyde	175	Neg.
	Anisaldehyde	175	Neg.
2-Methylthiazole-4-carboxylic	Benzaldehyde	178	Neg.
	Anisaldehyde	178	Neg.
o-Nitrobenzoic	Benzaldehyde	175	Neg.
	Anisaldehyde	175	Neg.
2,4-Dinitrobenzoic	Benzaldehyde	165	Neg.
	Anisaldehyde	165	Neg.

TABLE III

HAMMICK REACTIONS ON METHYL SUBSTITUTED PICOLINIC ACIDS IN 30 GRAMS OF ANISALDEHYDE AND 30 GRAMS OF *p*-CYMENE

Methyl substituted picolinic acid[a]	Product, *p*-methoxyphenylcarbinol	Temp., °C.	Yield, Grams	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3-Methyl	3-Methylpyridyl-	165	2.8	35	68	73.36	73.23	6.55	6.39
4-Methyl	4-Methylpyridyl-	173	4.9	53	96	73.36	73.10	6.55	6.50
5-Methyl	5-Methylpyridyl-	177	4.3	47	75	73.36	73.21	6.55	6.44
6-Methyl	6-Methylpyridyl-	170	5.2	57	77	73.36	73.53	6.55	6.58
4,6-Dimethyl	4,6-Dimethylpyridyl-	174	5.4	49	95	74.07	74.25	6.76	6.57

[a] 5.5 grams in each case except for 4,6-dimethylpicolinic acid where 6 g. was used.

tained in *p*-cymene. These findings are in agreement with those previously reported by Tilford.[3] Shelton and Van Campen on the effect of solvents on this reaction. The experimental procedure was the same as that employed by Hammick.[1] The yields utilizing *p*-cymene as solvent for the reaction are reported under yield as (b) in Table I.

p-Nitrobenzaldehyde, 2,4-dinitrobenzaldehyde, cinnamaldehyde and *p*-dimethylaminobenzaldehyde gave negative results both with and without the addition of solvents.

In an attempt to extend the reaction to acids other than those successfully employed by Hammick, the reaction was carried out on the thiazole, pyrimidine and nitrobenzoic acids listed in Table II. The reactions were carried out in anisaldehyde and, where the decarboxylation temperature of the acid was low enough, in benzaldehyde. All of the acids gave negative results in that they did not yield the expected carbinol, a coupling product between the decarboxylated acid and the carbonyl compound. Hammick[1] has shown that 2,4,6-trinitrobenzoic acid gives a negative reaction.

The reaction was also carried out on various methyl substituted picolinic acids, utilizing anisaldehyde as the carbonyl reactant and *p*-cymene as the solvent. The results are reported in Table III. All of the methyl substituted picolinic acids gave a positive Hammick reaction and the expected coupling products.

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(3) C. H. Tilford, R. S. Shelton and M. S. Van Campen, THIS JOURNAL, **70**, 4001 (1948).

Reactions of Ethylenimines. IV. With Carbon Disulfide

BY LEALLYN B. CLAPP AND JOHN W. WATJEN[1]

RECEIVED JULY 24, 1952

In repeating Gabriel's[2,3] synthesis of a 2-thiothiazolidone from an ethylenimine and carbon disulfide in ether, a 27% yield (Gabriel reported no yields) of 4,4-dimethyl-2-thiothiazolidone was ob-

(1) Taken in part from the Senior Thesis of John W. Watjen, Brown University, June, 1952.

(2) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(3) S. Gabriel and C. F. von Hirsch, *ibid.*, **29**, 2747 (1896).

TABLE I

2-THIOTHIAZOLIDONES

Substituents	M.p., °C.	Yields From ethylen-imine	Yields From amino alcohol	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
....	104.8–105.1		58[a]						
4-Methyl	99.0–99.5[b]	64	76						
5-Methyl	91.0–91.5[c]		70						
4,4-Dimethyl[d]	93.4–93.8	83.5		40.78	41.06	6.16	6.37	9.51	9.34
4.4-Dimethyl[d]	117.8–118.3		71.5		41.13		6.18		9.42, 9.28
4-Ethyl[e]	48.8–49.4	71.5	97	40.78	41.11	6.16	6.35	9.51	9.84
[f]	84.6–85.2		79	45.77	45.37	6.92	7.03	10.68	10.65

[a] Stevenson, ref. 4, reported a 95% yield. [b] Ref. 5, m.p. 98.5–99°. [c] C. Y. Hopkins, *Can. J. Research*, **20**B, 268 (1942), reported the m.p. 93–94°, yield "poor"; ref. 5, m.p. 88–89°. [d] Two crystalline forms. See Experimental part. [e] See ref. 6b. Analysis not published previously. [f] 5-Ethyl-2-thioöxazolidone.

TABLE II

3-*p*-NITROBENZOYL-2-THIOTHIAZOLIDONES

Substituent	M.p., °C.	Mol. formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
......	162.6–163.2	$C_{10}H_8N_2S_2O_3$	44.76	44.89	3.01	3.31
4-Methyl	159.0–160.0	$C_{11}H_{10}N_2S_2O_3$	46.79	46.83	3.57	3.82
5-Methyl	139.0–139.2	$C_{11}H_{10}N_2S_2O_3$	46.79	47.04	3.57	3.89
4,4-Dimethyl[a]	168.0–168.5	$C_{12}H_{12}N_2S_2O_3$	48.63	48.55	4.08	4.30
[b]	172.4–173.6	$C_{12}H_{13}NS_2O$	57.34	57.52	5.21	5.34
4-Ethyl	121.6–122.4	$C_{12}H_{12}N_2S_2O_3$	48.63	48.41	4.08	4.34
[c]	92.2–93.6	$C_{12}H_{12}N_2SO_4$	51.42	50.83	4.32	4.52

[a] *Anal.* Calcd.: N, 9.45. Found: N, 9.51. [b] 3-Benzoyl derivative. *Anal.* Calcd.: N, 5.57. Found: N, 5.52. [c] 3-*p*-Nitrobenzoyl-5-ethyl-2-thioöxazolidone. *Anal.* Calcd.: N, 10.00 Found: N, 10.36.

tained from 2,2-dimethylethylenimine. The low yield left in doubt the fate of the remainder of the ethylenimine. However, without solvent and under pressure following the work of Stevenson[4] the yield of 4,4-dimethyl-2-thiothiazolidone was increased to 83.5%; two other unsymmetrical ethylenimines gave the corresponding 4-alkyl-2-thiothiazolidones in somewhat lower yields (Table I). One may conclude that the three-membered ethylenimine ring opens predominantly at the primary carbon with carbon disulfide under favorable conditions.

Evidence for the structure of the 4-alkyl-2-thiothiazolidones as given by Gabriel and Ohle[5] has been corroborated in an independent way by synthesis from the appropriate aminoalcohol.[4] Application of Stevenson's method again gave good yields of 2-thiothiazolidones in all but one case. While 1-amino-2-propanol gave 70% 5-methyl-2-thiothiazolidone, the corresponding thioöxazolidone was obtained in 79% yield from 1-amino-2-butanol. Ettlinger[6] has suggested a mechanism in which the proportion of thiothiazolidone formed from an amino alcohol should diminish with increasing hindrance of the hydroxyl group.[7] Comparison of these results with those of Rosen[8] on the reaction of amino alcohols (including 1-amino-2-propanol and 2-methyl-2-amino-1-propanol) with carbon disulfide in alcoholic alkali shows that formation of thiothiazolidones is favored by absence of the alkaline solvent.

The properties of the *p*-nitrobenzoyl derivatives of these 2-thiothiazolidones are recorded in Table II. That these derivatives should be called N-acyl[9] rather than S-acyl compounds seems very probable from the infrared spectra. In agreement with Ettlinger,[10] the infrared spectra of 4,4-dimethyl-2-thiothiazolidone indicate the presence of an N–H stretching band at 3.24 μ and the absence of a band due to C═N in the region 6–6.3 μ. This normally strong C═N absorption band is also missing in the benzoyl derivative of 4,4-dimethyl-2-thiothiazolidone and the three *p*-nitrobenzoyl derivatives of 5-ethyl-2-thioöxazolidone, 2-thiothiazolidone and 4,4-dimethyl-2-thiothiazolidone. Strong absorption bands do occur in these four compounds at 5.87, 5.88, 5.92 and 5.91 μ, respectively, which in the absence of a C═N bond may be interpreted[11a] as due to carbonyl groups on nitrogen.[11b]

Experimental[12]

4,4-Dimethyl-2-thiothiazolidone.—All the compounds reported in Table I were prepared in a stainless steel cylinder 15 inches long, one inch in diameter, and closed by a screw-cap carrying a lead washer. Ten grams of carbon disulfide was placed in the cylinder and cooled by a Dry Ice–isopropyl alcohol-bath while 5.0 g. of 2,2-dimethylethylenimine was added dropwise. After allowing the mixture to cool 15 minutes longer, the cylinder was sealed and transferred to the autoclave at 100° for 6 hours heating. Hydrogen sulfide was allowed to escape from the cylinder at the end of the heating period after cooling it to room temperature.

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[4] H. B. Stevenson, U. S. Patents 2,364,398–9 (1944).

[5] S. Gabriel and H. Ohle, *Ber.*, **50**, 840 (1917).

[6] M. G. Ettlinger, THIS JOURNAL, **72**, 4792 (1950).

[7] Compare J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

[8] A. A. Rosen, THIS JOURNAL, **74**, 2994 (1952).

[9] Suggested by Dr. Martin G. Ettlinger who cited the following references to support the conclusion that acylation of thioamides derived from carbonic acid yields N-acyl amides: H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **24**, 189 (1900); M. Delepine, *Bull. soc. chim.*, [3] **29**, 48 (1903); A. E. Dixon and J. Hawthorne, *J. Chem. Soc.*, **91**, 122 (1907); A. E. Dixon and J. Taylor, *ibid.*, **117**, 720 (1920).

[10] M. G. Ettlinger, THIS JOURNAL, **72**, 4699 (1950).

[11] (a) The authors are indebted to Mr. Charles E. Grabiel, Brown University, for taking and interpreting the infrared spectra. (b) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 24 ff.

[12] All melting points are corrected. Analyses by S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

Then the contents of the cylinder were dissolved in warm 5% sodium hydroxide. charcoal was added to the warm yellow solution, and the mixture was allowed to stand 15 minutes. The filtered solution was cooled to 5° in ice and cold dilute hydrochloric acid was added dropwise with stirring until the solution was neutral to litmus. (Ammonium chloride solution was preferred for an acid near the end-point.) The 4,4-dimethyl-2-thiothiazolidone, collected on a buchner funnel, weighed 8.0 g. after drying. By extracting the water solution with ether, 0.66 g. more was obtained; total yield 8.66 g., 83.5%, m.p. 87–91°. An analytical sample was obtained by recrystallization from 95% ethanol and sublimation at 60–75° (0.4 mm.), m.p. 93.4–93.8°.

By the procedure just described 9.5 g. of 2-methyl-2-amino-1-propanol was sealed with 20 g. of carbon disulfide in the stainless steel cylinder. After working up the resulting product in the same way, 11.25 g. of 4,4-dimethyl-2-thiothiazolidone, m.p. 112–116°, was obtained. An analytical sample obtained in the same way as that just described gave a m.p. 117.8–118.3°.[8,13]

The anomaly in the melting points of the two samples of 4,4-dimethyl-2-thiothiazolidone appears to be a case of dimorphism in which the two crystalline forms have nearly the same stability. The mixed melting point was 93–116°. Upon recrystallizing 1 g. of a 1:1 mixture of the two forms from 95% ethanol. 0.80 g. was obtained of m.p. 94–115° and a second crop by adding a few drops of water, of 0.12 g., m.p. 91–93°. The higher melting, less soluble crystals were almost spheroidal in shape. bounded by numerous surfaces while the lower melting form may be described as elongated plates. Seeding the melt of the lower melting crystals with the higher gave only a partial conversion to the second form, with a new m.p. 93–110°. The two samples gave the same 3-benzoyl derivative. the same 3-*p*-nitrobenzoyl derivative. and identical infrared spectra in carbon tetrachloride solution.

The acyl derivatives described in Table II were prepared by the standard Schotten–Baumann procedure and recrystallized from 95% ethanol in which they were all sparingly soluble. The thiothiazolidones except 4-ethyl-2-thiothiazolidone were easily sublimed at low pressure for analytical samples. The thioöxazolidone decomposed upon sublimation.

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(13) J. P. English. American Cyanamid Co., reports m.p. 115–116°; private communication.

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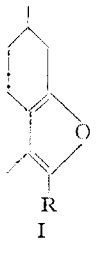
Substituted Menthofurans

BY RICHARD H. EASTMAN AND ROSS P. WITHER

RECEIVED SEPTEMBER 26, 1952

In continuing the study of the autoxidation of menthofuran[1] (I, R = H) we have prepared piperidinomethylmenthofuran (I, R = $CH_2NC_5H_{10}$), menthofuroic acid (I, R = COOH) and its anilide (I, R = $CONHC_6H_5$), and menthofurfuryl alcohol (I, R = CH_2OH) to determine whether the presence of the α-hydrogen atom on the furan nucleus is requisite for the production of the remarkable deep blue color that develops in solutions of menthofuran undergoing autoxidation. The piperidinomethyl compound and menthofurfuryl alcohol are readily autoxidized but do not show the blue color phenomenon. Menthofuroic acid and its anilide are stable towards autoxidation.



I

Experimental

Piperidinomethylmenthofuran (I, R = $CH_2NC_5H_{10}$).—A solution of 5.1 g. of menthofuran,[2] 1.5 g. of piperidine hydrochloride and 1.5 g. of paraformaldehyde in 50 ml. of absolute alcohol was heated under reflux for 1 hour. Removal of most of the solvent under reduced pressure caused the separation of 4.4 g. of white solid of m.p.[3] 202-204° (dec.). Crystallization from an alcohol–hexane–ethyl acetate mixture gave 4.1 g. of piperidinomethylmenthofuran hydrochloride of m.p. 208.5–209° (dec.). An additional 3.0 g. of pure material was isolated from the reaction liquor by concentration, bringing the yield to 84% of the theory.

Anal.[4] Calcd. for $C_{16}H_{26}ClNO$: C, 67.70; H, 9.23; Cl, 12.50. Found: C, 67.45; H, 9.13; Cl, 12.17.

The presence of nitrogen was established by sodium fusion; and the ultraviolet absorption spectrum showed $\lambda_{\max}^{\text{alc.}}$ 233 mμ (4.01) which is expected on the basis that menthofuran shows $\lambda_{\max}^{\text{alc.}}$ 219.5 mμ (3.78).

The free base was generated by treating the hydrochloride with an excess of 20% sodium carbonate solution. It was obtained as a colorless, water-insoluble oil of b.p. 189.5–191.5° at 20 mm.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66; neut. equiv., 247. Found: C, 77.72; H, 10.20; N, 5.68; neut. equiv., 236.

The ultraviolet absorption showed $\lambda_{\max}^{\text{alc.}}$ 228 mμ (4.10) and 294 mμ (1.28). The weak absorption at 294 mμ is ascribed to an autoxidation product of the base since the intensity of absorption at this wave length increased to log ε 2.30 on exposure of the free base to air during 14 days.

The picrate of the base constituted bright-yellow crystals of m.p. 139.5–140° after crystallization from aqueous alcohol.

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92. Found: C, 55.48; H, 5.85.

Menthofuroylanilide (I, R = $CONHC_6H_5$).—Menthofuran (28 g.) and phenyl isocyanate (45 g.) were heated with protection from moisture at 160° for 24 hours. Upon cooling the reaction mixture 25 g. of yellowish crystals separated which were crystallized from aqueous alcohol to give 24 g. of white needles of m.p. 156–156.5°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.84; H, 7.11. Found: C, 75.56; H, 6.89.

This substance is assigned the structure of menthofuroyl anilide on the basis of its analysis. insolubility in acid and base. and its ultraviolet absorption which showed $\lambda_{\max}^{\text{alc.}}$ 292 mμ (4.40) and great similarity to that of furoyl anilide, $\lambda_{\max}^{\text{alc.}}$ 276 mμ (4.27).

In subsequent experiments, using carefully purified phenyl isocyanate, it was discovered that the Friedel-Crafts reaction did not proceed well unless a trace of hydrogen chloride was added to the reaction mixture. The quantity of hydrogen chloride in ordinary samples of phenyl isocyanate was sufficient to catalyze the reaction.

Menthofuroic Acid (I, R = COCH).—Attempts to hydrolyze menthofuroyl anilide using 6 *N* hydrochloric acid. 10% aqueous or alcoholic potassium hydroxide, and the methods of Baum[5] and of Marquis[6] for furoyl anilide returned the anilide unchanged. Hydrolysis of the anilide (1.0 g.) with barium hydroxide octahydrate (4.7 g.) in 25 ml. of ethylene glycol at 140° for 4 hours gave a 76% yield (0.55 g.) of a white acidic solid of m.p. 179–179.5° (dec.) which is assigned the structure of menthofuroic acid on the basis of its analysis. decomposition into menthofuran by heat, and ultraviolet absorption spectrum which showed $\lambda_{\max}^{\text{alc.}}$ 270 mμ (4.24) to be compared with that for furoic acid $\lambda_{\max}^{\text{alc.}}$ 246 mμ (4.05).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98: H, 7.44.

Menthofurfuryl Alcohol (I, R = CH_2OH).—Ten grams of menthofuroic acid in 150 ml. of dry ether was added dropwise to 130 ml. of ether containing 2.42 g. of lithium aluminum hydride. Following the addition, stirring was continued for 15 minutes. The unreacted hydride was decomposed by the addition of water and then 80 ml. of 10% sulfuric acid was added. The ether layer was separated, washed with dilute sodium bicarbonate solution and dried

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(1) R. B. Woodward and R. H. Eastman. THIS JOURNAL. **72**. 399 (1950).

(2) R. H. Eastman. *ibid.*. **72**. 5313 (1950).

(3) Melting points are corrected.

(4) Analyses by Microchemical Specialties Co.. Berkeley. California.

(5) E. Baum. *Ber.*. **37**. 2949 (1904).

(6) R. Marquis. *Ann. chim. phys.*. [8] **4**. 279 (1905).

over potassium carbonate. The ether was evaporated to leave a residue of 6.1 g. of a base-insoluble, white, crystalline solid of m.p. 50°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.54; H, 8.95.

This substance is assigned the structure of menthofurfuryl alcohol on the basis of its method of preparation and analysis. Exposure of it to the atmosphere, even momentarily, caused discoloration and rapid liquefaction and tar formation. Hence, the ultraviolet absorption of the material, $\lambda_{\max}^{\text{alc.}}$ 228 mμ (3.96), 294 mμ (2.31) cannot be regarded as indicative of its structure.

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Anomalies in the Vapor Phase Ozonolysis of Cyclohexene

BY RICHARD H. EASTMAN AND R. M. SILVERSTEIN

RECEIVED SEPTEMBER 26, 1952

Ozonolysis of cyclohexene in the liquid phase has been shown[1] to produce adipic acid and the corresponding half and dialdehydes. The renewed interest in the ozonolysis reaction[2] prompts this preliminary report of a study of the vapor phase ozonolysis of cyclohexene which has been found to produce the abnormal products formic acid and *trans*-1,2-cyclohexandiol in small yield in addition to adipic acid as the major product.

A. **Materials and Method.**—The cyclohexene (Phillips Petroleum) was redistilled 99 mole per cent. material of infrared absorption[3] identical with that reported.[4]

For the preparation of cyclohexene ozonide a stream of dry nitrogen flowing at a rate of 50 ml. per minute was passed through a thermostated hydrocarbon bubbler to carry cyclohexene vapor into a reaction tube at 0.16 millimole per minute. Ozone entered the reaction tube at the rate of 0.10 millimole per minute in a dry, ozonized oxygen stream flowing at the rate of 150 ml. per minute. At the confluence of the streams an aerosol was produced as a heavy smoke. As the reaction proceeded, a viscous, colorless condensate appeared on the walls of the reactor tube and slowly ran down into a trap provided for its collection.

The ultraviolet absorption spectrum of the ozonide showed only general absorption of low intensity in the 220–310 mμ region. Absorption in the carbonyl region (270–300 mμ) was specifically absent in samples taken with precaution to avoid moisture but appeared in samples exposed to laboratory air or treated with water.

The infrared absorption of the ozonide showed strong bands at 2.95, 3.40 and 5.82 μ which are attributed to OH, CH and C=O[5] vibrations, respectively. The 6–13 μ region showed only general absorption with a suggestion of discrete bands at 8.5 and 9.1 μ.

As the ozonide stood, crystals of adipic acid were slowly deposited. The yield of adipic acid never exceeded 50% in a number of experiments, the remainder of the material being an intractable, alkali-soluble, viscous oil.

Titration of the ozonide with sodium hydroxide against phenolphthalein gave neutral equivalents of 269, 261 and 243. A Zerewitinoff determination in cineole as solvent showed 0.75 active H per $C_6H_{10}O_3$ unit. Iodometry showed an active oxygen content of 1.8%. Analysis of the ozonide gave: C, 52.0, 52.2, 52.4; H, 7.9, 8.5, 8.9. Calcd. for $C_6H_{10}O_3$: C, 55.4; H. 7.7.

B. **Isolation of Formic Acid.**—Cyclohexene ozonide (10.6 g.) was distilled into two traps in series, one at 0° and the second at −78°. The pressure was slowly lowered to 2 mm. as the pot temperature was raised to 90°. The contents of the traps were found to be aqueous formic acid solutions. Identity was established by infrared absorption and by the hydroxamic acid–ferric ion color reaction. The quantity of formic acid was determined by titration and corresponded to 10% of the theoretical based upon one mole per mole of $C_6H_{10}O_3$ (0.37 g.).

C. **Isolation of *trans*-1,2-Cyclohexandiol.**—Cyclohexene ozonide (8.7 g.) was decomposed by heating under reflux with water (40 ml.) for 2.5 hours. The hydrolysate was brought to *p*H 9 by the addition of standard sodium hydroxide corresponding to 0.8 carboxyl group per $C_6H_{10}O_3$; and, the alkaline solution was continuously extracted with ether for 10 hours. Evaporation of solvent left 1.3 g. of yellowish oil which was distilled to give 0.47 g., b.p. 70–110° at 14 mm. which was presumably largely cyclopentenealdehyde-1 since it showed $\lambda_{\max}^{\text{alc}}$ 235 mμ, and formed a semicarbazone[1] of m.p. 208–209°; and, 0.2 g. b.p. 110–170° at 1 mm. which solidified on being cooled. Three crystallizations of the solid from benzene plus hexane gave 0.1 g. of white plates of m.p. 100–102.5°.

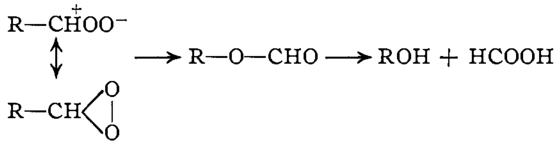
Anal. Found: C, 61.9; **H**, 10.4. Calcd. for $C_6H_{12}O_2$: C, 62.1; H, 10.4.

The infrared absorption of this material was identical with that of an authentic sample[6] of *trans*-1,2-cyclohexandiol, and no depression was observed in a mixed melting point determination.

Discussion

These results support the earlier observation[7] that the reaction of ozone with olefins in the vapor phase produces "ozonides" having different properties than those produced in condensed systems. Thus, the absence of ketone or aldehyde absorption in the ultraviolet is to be contrasted with the frequent appearance of these groups in liquid phase ozonolyses.[8] Further, in a direct comparison of the infrared absorption of the liquid phase product, prepared according to Harries,[1] and the vapor phase product, although both showed a strong band at 5.82 μ, the band at 2.92 μ was absent in the liquid phase product. In addition there was no correspondence in the 6–13μ region.

A possible source of formic acid in the distillate from the vapor phase reaction product is suggested by application of the mechanism proposed by Criegee[8] as



$$R-\overset{+}{C}HOO^- \longleftrightarrow R-CH\langle O_2 \rangle \longrightarrow R-O-CHO \longrightarrow ROH + HCOOH$$

The 1,2-shift which results in the formic ester has further analogy in the formation of lactones from ketones on treatment with peracids.[9] Alternatively, an ozone-catalyzed free radical oxidation of cyclohexene at the position allylic to the double bond may occur with the production of 2-cyclohexenol. Normal ozonolysis of the cyclohexenol would lead to formic acid.[10]

The isolation of *trans*-1,2-cyclohexandiol is of

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(1) C. Harries and R. Seitz, *Ann.*, **410**, 24 (1915).

(2) B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3855, 3861 (1952); references 5 and 8.

(3) Spectra were determined with a Perkin-Elmer model 12-c spectrophotometer in the region 2.5 to 12 μ using rock salt optics.

(4) A.P.I. Index.

(5) E. Briner, *et al.*, have found a band at 5.8 μ in the spectra of a large number of ozonized solutions of hydrocarbons, including cyclohexene; *Helv. Chim. Acta*, **35**, 340, 345, 353 (1952).

(6) J. B. Senderens and J. Aboulenc, *Comp. rend.*, **173**, 1367 (1921).

(7) E. Briner, *Helv. Chim. Acta*, **12**, 154, 529 (1929); E. Briner and S. de Nimitz, *ibid.*, **21**, 748 (1938).

(8) R. Criegee, 120th Meeting of the American Chemical Society, New York, N. Y., Sept. 7, 1951, Abstracts 22M.

(9) W. E. Doering and L. Speers, THIS JOURNAL, **72**, 5515 (1950).

(10) J. E. Leffler, *Chem. Rev.*, **45**, 400 (1949). This alternative was suggested by one of the Referees.

interest in reference to the failures to obtain 1,2-diols by reduction of "ozonides" prepared in the liquid phase.[11] The *trans* nature of the diol would seem to preclude its formation by reduction of an ozonide of the Harries structure, and would seem rather to indicate that the immediate precursor of the diol was cyclohexene oxide.

We express our appreciation for support of this investigation by the Western Oil and Gas Association.

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(11) A. Rieche, "Alkylperoxyde und Ozonide," Edwards Brothers, Inc., Ann Arbor, Mich., 1945 (1931), p. 132.

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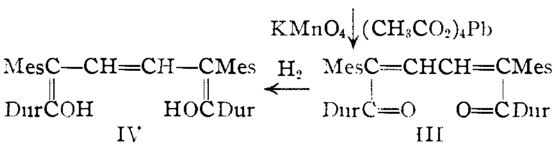
A New Stilbenediol Vinylog

BY REYNOLD C. FUSON AND RICHARD F. HEITMILLER

RECEIVED OCTOBER 29, 1952

Duryl α-mesitylvinyl ketone (I) has been found to undergo bimolecular reduction with the binary mixture, Mg + MgI_2,[1] to yield the stable dienol, 1,6-diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol (II). Oxidation of the dienol with lead tetraacetate converted it to the corresponding hexadienedione (III). Treatment with potassium permanganate gave the dione accompanied by the original vinyl ketone (I).

Catalytic hydrogenation of the diketone (III) produced the enediol, 1,6-diduryl-2,5-dimesityl-1,3,5-hexatriene-1,6-diol (IV). Thus it has been established that duryl α-mesitylvinyl ketone (I) yields a stable vinylog of didurylacetylene glycol.[2] The new series of compounds, derived from duryl α-mesitylvinyl ketone (I), is very similar to that produced earlier from mesityl α-mesitylvinyl ketone.[3]



Duryl α-Mesitylvinyl Ketone.—The method was a modification of that of Fuson and Sperati.[4] A mixture of 3.9 g. of duryl 2,4,6-trimethylbenzyl ketone, 4.0 g. of paraformaldehyde, 2.0 g. of potassium carbonate and 70 ml. of ethanol was stirred under reflux overnight. The reaction was promoted by the addition of 0.20 g. of powdered black ferric oxide. The solution was poured into ice and acidified with dilute (1:10) hydrochloric acid. The white gummy crystals which formed were washed with cold ethanol and recrystallized from ethanol; m.p. 159°, yield 80%. The reported melting point is 159–160°.[4]

1,6-Diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol.—To a mixture of 1.92 g. of magnesium, 40 ml. of dry ether and 80 ml. of dry benzene was added, with stirring, 9.8 g. of iodine. When the iodine color had disappeared, 12.25 g. of solid duryl α-mesitylvinyl ketone was added within 1 minute. The solution was stirred and heated under reflux for 3 hours, cooled and decomposed with iced hydrochloric acid. The crude product, isolated by usual procedures, weighed 11.6 g., m.p. 189–192°. The pure compound melts at 196°.

Anal.[5] Calcd. for $C_{44}H_{54}O_2$: C, 85.94; H, 8.52. Found: C, 86.33; H, 8.83.

1,6-Diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol Diacetate.—A solution of 2.0 g. of the diol and 15 ml. of acetic anhydride was heated under reflux for 2 hours and poured into water. The diacetate separated from benzene as colorless crystals; m.p. 209°, yield 2.0 g. It was purified by further crystallization from benzene; m.p. 220–221°.

Anal. Calcd. for $C_{48}H_{58}O_4$: C, 82.47; H, 8.36. Found: C, 82.67; H, 8.33.

The infrared spectrum[6] has bands assignable to vinyl ester (1751 cm.$^{-1}$), mesityl and duryl skeletal ring vibrations (1611 cm.$^{-1}$) and mesityl hydrogen atoms which are out of the plane of the ring (855 cm.$^{-1}$).

The Reaction of 1,6-Diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol with Potassium Permanganate.—A solution of 1.9 g. of potassium permanganate in 250 ml. of acetone was added over a period of 0.5 hour, with stirring, to a solution of 5.0 g. of the diol in 160 ml. of acetone. The manganese dioxide was removed by filtration and extracted in a Soxhlet extractor until the extracting solution was no longer yellow. The organic solutions were combined and concentrated to a volume of 150 ml. The excess permanganate was removed by filtration as manganese dioxide, and the clear yellow solution was concentrated to 25 ml. and cooled. The canary-yellow product was washed with methanol, the washings being added to the main filtrate. The crude 1,6-diduryl-2,5-dimesityl-2,4-hexadiene-1,6-dione weighed 2.1 g., m.p. 253–257°. It was recrystallized from benzene; m.p. 265–266°.

The infrared spectrum has absorption bands assignable to a conjugated ketone grouping (1656 cm.$^{-1}$) and mesityl hydrogen atoms out of the plane of the ring (857 cm.$^{-1}$).

Anal. Calcd. for $C_{44}H_{50}O_2$: C, 86.51; H, 8.25. Found: C, 86.28; H, 8.21.

The mother liquor was evaporated to dryness and subjected to fractional crystallization from methanol. In this manner there was isolated an additional 0.2 g. of the yellow dione (m.p. 263–264°) and 1.2 g. of a colorless compound (m.p. 159°) identified by a mixed melting point as duryl α-mesitylvinyl ketone.

Reaction of 1,6-Diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol with Lead Tetraacetate.—To a hot solution of 5.0 g. of the diol in 100 ml. of benzene was added, with stirring, 10.5 g. of lead tetraacetate. The mixture was stirred under reflux for 14 hours. The yield of 1,6-diduryl-2,5-dimesityl-2,4-hexadiene-1,6-dione (m.p. 265–266°) was 2.3 g. From the mother liquor was isolated 0.4 g. of duryl α-mesitylvinyl ketone, m.p. 159°.

1,6-Diduryl-2,5-dimesityl-1,3,5-hexatriene-1,6-diol. (A).—A solution of 0.2 g. of the diketone in 150 ml. of benzene was shaken with a platinum oxide catalyst and hydrogen at atmospheric pressure until the yellow color had disappeared. The catalyst was removed by filtration and the solution was concentrated to a small volume and cooled. The resulting colorless diol melted at 236–237°. When the pure compound was exposed to the atmosphere it assumed a brownish color, and after one week the melting point had dropped to 231–232°.

The infrared spectrum has bands attributable to hydroxyl (3476 cm.$^{-1}$), mesityl and duryl skeletal ring vibrations (1611 cm.$^{-1}$), C–O–H (1142 cm.$^{-1}$), mesityl hydrogen out of the plane of the ring (850 cm.$^{-1}$) and double bond hydrogen (869.5 and 1007 cm.$^{-1}$). Absorption at 1282 cm.$^{-1}$ indicates the possible presence of an epoxy structure, which might account for the manner in which the compound decomposes when exposed to air.

Anal. Calcd. for $C_{44}H_{52}O_2$: C, 86.22; H, 8.55. Found: C, 86.38; H, 8.46.

(B).—To a solution of 0.5 g. of the diketone in 75 ml. of hot glacial acetic acid was added 3.0 g. of zinc dust. The

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(1) M. Gomberg and W. E. Bachmann, THIS JOURNAL, **49**, 236 (1927).

(2) R. C. Fuson and S. C. Kelton, Jr., *ibid.*, **63**, 1500 (1941).

(3) R. C. Fuson, D. J. Byers and A. I. Rachlin, *ibid.*, **64**, 2891 (1942).

(4) R. C. Fuson and C. A. Sperati, *ibid.*, **63**, 2643 (1941).

(5) Microanalyses by Miss Emily Davis, Mrs. Katherine Pih and Mrs. Jeanne Fortney.

(6) The infrared spectra were observed and interpreted by Miss Elizabeth Petersen.

mixture was heated on a steam-bath for 1 hour and filtered while hot. Cooling of the filtrate caused the separation of 0.4 g. of a brownish crystalline solid which melted, after being washed with water, at 224–229°. Recrystallized from ethanol, the product was colorless and melted at 236–237° alone or when mixed with a sample of the material obtained by method **A**.

1,6-Diduryl-2,5-dimesityl-1,3,5-hexatriene-1,6-diol Diacetate.—A solution of 0.5 g. of the diol in 25 ml. of acetic anhydride was heated under reflux for 90 minutes. Cooling caused the separation of 0.49 g. of white needles, m.p. 252–255°. The diacetate was purified by recrystallization from glacial acetic acid; m.p. 275°.

Anal. Calcd. for $C_{48}H_{56}O_4$: C, 82.71; H, 8.09. Found: C, 82.41: H, 8.26.

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The Polarographic Behavior of Methyl Vinyl Ketone and Methyl Vinyl Sulfone[1]

BY C. W. JOHNSON, C. G. OVERBERGER AND W. J. SEAGERS

RECEIVED OCTOBER 28, 1952

Most α,β-unsaturated carbonyl compounds exhibit, on polarographic reduction, two waves which have been considered to be due to the reduction of the enol form of the compound (*p*H dependent) followed by the reduction of the double bond (*p*H independent).[2] If the corresponding α,β-unsaturated sulfone exhibited similar polarographic behavior, the reduction could plausibly be expected to proceed through a similar mechanism involving the enol form if it is assumed that this is the current picture of the reduction of α,β-unsaturated carbonyl compounds. In order for the sulfone to form the enol, the sulfur octet would have to enlarge to hold ten electrons. This expansion of the sulfur octet has been the subject[3] of much controversy. Thus, it seemed of interest to examine the polarographic behavior of an α,β-unsaturated sulfone and the corresponding α,β-unsaturated ketone.

The two compounds selected for investigation were methyl vinyl sulfone and methyl vinyl ketone. Only the ketone has been reported as being polarographically reducible.[4] Only one wave was observed at −1.43 v. *vs.* S.C.E. in 0.1 *M* potassium chloride solution.

Experimental

Apparatus.—All polarograms were recorded with a Sargent Polarograph Model XXI. The linearity of the potential dial was checked by means of a Leeds and Northrup Potentiometer. Half-wave potentials were read directly from the chart and were calculated to be accurate within 15 millivolts. Corning marine barometer tubing was used for the capillary which had a value of 1.51 mg.$^{2/3}$ sec.$^{1/6}$ for the capillary constant at open circuit in 0.5 *M* potassium chloride at 25°. The water-jacketed, H-type cell[5] with attached saturated calomel electrode, was maintained at 25 ± 0.2° by circulating water through the jacket from an external constant temperature bath. The *p*H of all solutions were measured with a Beckman Model G *p*H Meter.

Materials.—The methyl vinyl ketone was obtained from E. I. du Pont de Nemours and Co. as 85% azeotrope with water having about 0.5% acetic acid and 0.1% hydroquinone present. Since neither of these compounds is reduced at the dropping mercury electrode, the ketone solution was used without further purification. The methyl vinyl sulfone was prepared by the method of Price[6] and after careful purification had the following physical constants; b.p. 110° (18 mm.) (literature value[6] b.p. 115–117° (19 mm.)) and $n^{22}D$ 1.4262. Appropriate quantities of the organic compounds were dissolved in 95% ethanol and an aliquot diluted with aqueous buffer to give a final solution 0.5 m*M* in reducible species and 10% in ethanol. The buffer was 0.1 *M* with respect to buffering constituents (acetic, boric and phosphoric acids with various amounts of 1 *M* sodium hydroxide in order to cover the *p*H range 2 to 12) and 0.5 *M* with respect to potassium chloride in order that a high ionic strength (0.62 *M*) might be maintained.[7] Tank nitrogen, purified by passage through gas bubblers (one, containing concentrated sulfuric acid; a second, an alkaline solution of pyrogallol; and a third, a sample of cell solution) was bubbled through the solution in the polarographic cell for five minutes before polarographing. Polarograms were recorded over the potential range 0 to −2 volts *vs.* S.C.E. at a suitable sensitivity. The half-wave potentials were determined by the usual graphical method.

Results and Discussion

The half-wave potential *vs.* *p*H curves for both ketone and sulfone are shown in Fig. 1. It is seen that methyl vinyl ketone exhibits the polarographic behavior expected of an α,β-unsaturated carbonyl compound, *i.e.*, two waves, one *p*H dependent and one *p*H independent. Methyl vinyl sulfone, on the other hand, exhibits only one wave which is *p*H independent indicating that the double bond is the only group present that is polarographically reducible in the potential range available. This lack of reduction of the sulfone group may be explained by the inability of the sulfone group to form an appreciable concentration of conjugate acid (see following paragraph).

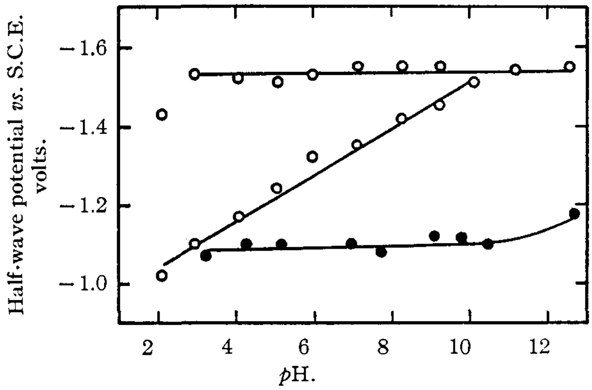

Fig. 1.—Half-wave potential *vs.* *p*H curves for methyl vinyl sulfone (closed circles) and methyl vinyl ketone (open circles).

Thus, another possible mechanism of the reduction of the α,β-unsaturated carbonyl group could involve, rather than the reduction of the enol form, the reduction of the conjugate acid of the keto form I which would be expected to be *p*H dependent.

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(1) Abstracted from the thesis of C. W. Johnson, submitted in partial fulfillment of the requirements of the degree Master of Science in Chemistry, June, 1952.

(2) S. Wawzonek, *Anal. Chem.*, **21**, 62 (1949).

(3) For an excellent discussion of this question see H. P. Koch and W. E. Moffitt, *Trans. Faraday Soc.*, **47**, 7 (1951). In particular it is demonstrated that due to the geometry of the orbitals in linear α,β-unsaturated sulfone systems less expansion or less interaction of the electrons of the double bond and of the sulfone group is probable than in the cyclic α,β-unsaturated sulfone systems that are present in substituted thiophene-1-dioxides.

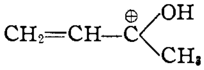
(4) E. I. Fulmer, J. J. Kolfenbach and L. A. Underkofler, *Ind. Eng. Chem., Anal. Ed.*, **16**, 469 (1944).

(5) J. C. Komyathy, F. Malloy and P. J. Elving, *Anal. Chem.*, **24**, 431 (1952).

(6) C. C. Price and J. Zomlefer, THIS JOURNAL, **72**, 14 (1950).

(7) P. J. Elving, J. C. Komyathy, R. E. VanAtta, C. S. Tang and I. Rosenthal, *Anal. Chem.*, **23**, 1218 (1951).

The second wave would again result from the reduction of the double bond. Thus, the nonreduction of the sulfone group could be attributed to the difficulty of forming appreciable concentrations of the conjugate acid of the sulfone (II) due to the inability of structures such as II-b to contribute proportionately to the resonance hybrid. It is, of course, possible that the conjugate acid reduces



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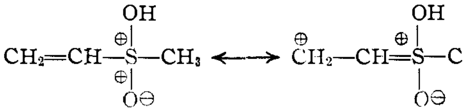

IIa IIb

with great difficulty and that this accounts for the difference in ease of reduction. The absence of acid catalysis in halogen addition to methyl vinyl sulfone[8] can also be ascribed to the absence of conjugation involving structures such as IIb.

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(8) I. R. C. McDonald, R. M. Milburn and P. W. Robertson, *J. Chem. Soc.*, 2836 (1950).

DEPARTMENT OF CHEMISTRY
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Low Temperature Heat Capacities of Inorganic Solids. XIII. Heat Capacity of Lithium Borohydride[1]

BY NATHAN C. HALLETT AND HERRICK L. JOHNSTON

RECEIVED MAY 24, 1952

Introduction

The only measurements of thermodynamic interest thus far reported on lithium borohydride are the heats of formation by Davis, Mason and Stegeman.[2] As part of the Cryogenic Laboratory program of measuring the thermodynamic properties of the boron hydrides and of the metallo borohydrides the heat capacity of solid lithium borohydride has been measured from 15 to 303°K.

Apparatus and Material

The heat capacity measurements were made in calorimeter No. 1, one of a group of seven calorimeters for the measurements of the heat capacity of solid materials. This calorimeter has been described in an earlier paper.[3]

The sample of lithium borohydride was obtained through the courtesy of the General Electric Research Laboratory at a reported purity of approximately 95%. The sample was purified and analyzed by the method of Davis, Mason and Stegeman,[2] except that all handling of the sample, including purifying, filling, sealing and emptying the calorimeter was done under an anhydrous nitrogen atmosphere in a dry-box. The resulting purity was found to be 99.7%. The calorimeter contained 9.9290 g. (0.4556 mole) of lithium borohydride.

Experimental Results

The experimental heat capacity data, summarized in Table I, follow a normal S-shaped curve.

TABLE I

MOLAR HEAT CAPACITY OF LITHIUM BOROHYDRIDE ($LiBH_4$)

Mol. wt. 21.79; 0.4556 mole

Mean T, °K.	C_p, cal./mole/deg.	Mean T, °K.	C_p, cal./mole/deg.
15.72	0.1781	225.36	15.65
19.37	.2484	231.97	15.96
21.76	.3369	238.75	16.30
23.64	.3981	244.35	16.59
25.39	.4723	249.53	16.74
27.40	.5546	250.48	16.83
30.71	.7642	254.66	17.02
34.28	.9532	255.97	17.12
38.04	1.226	259.50	17.28
42.41	1.585	260.63	17.353
46.88	2.027	262.14	17.45
51.67	2.374	264.87	17.63
56.55	2.854	266.59	17.70
61.06	3.310	267.60	17.73
62.08	3.384	269.11	17.94
67.12	3.892	270.41	17.96
72.79	4.390	272.45	18.07
78.65	5.072	272.82	18.21
84.98	5.755	272.96	18.24
86.23	5.894	274.47	18.24
92.82	6.516	277.65	18.44
99.93	7.168	278.32	18.50
107.76	7.895	278.71	18.53
115.93	8.618	280.25	18.75
124.42	9.324	283.77	18.87
132.35	9.975	284.15	18.90
140.02	10.49	284.76	18.95
147.33	11.08	288.74	19.10
155.32	11.631	288.75	19.12
164.09	12.21	289.20	19.18
172.37	12.67	293.43	19.48
180.82	13.13	294.27	19.50
188.84	13.63	296.95	19.62
196.83	14.06	298.50	19.74
204.66	14.50	299.20	19.74
212.05	14.91	299.47	19.80
218.86	15.28	302.88	20.02

Table II gives the heat capacity and derived thermodynamic functions for lithium borohydride at selected integral values of the temperature.

TABLE II

THERMODYNAMIC FUNCTIONS FOR LITHIUM BOROHYDRIDE ($LiBH_4$)

Temp., °K.	C_p, cal./mole/deg.	S^0, cal./mole/deg.	$(H_0^0 - H^0)/T$, cal./mole/deg.	$-(F^0 - H_0^0)/T$, cal./mole/deg.
15	0.152	0.0874	0.0515	0.0359
25	0.451	0.225	.144	.0811
50	2.235	1.013	.692	.322
75	4.709	2.373	1.606	.766
100	7.188	4.077	2.700	1.376
125	9.371	5.919	3.820	2.099
150	11.246	7.799	4.906	2.892
175	12.832	9.655	5.929	3.726
200	14.250	11.462	6.881	4.581
225	15.617	13.221	7.777	5.444
250	16.802	14.930	8.622	6.308
275	18.254	16.595	9.428	7.168
298.16	19.733	18.131	10.226	7.904
300	19.847	18.252	10.230	8.022

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[1] This work was suported in part by the Office of Naval Research under contract with The Ohio State University Research Foundation.

[2] W. Davis, L. Mason and G. Stegeman, Thermal Properties of Some Hydrides, Univ. of Pittsburgh, ONR Contract Number N6ORI-43, Task Order No. 1, Technical Report, Dec. 1, 1948.

[3] H. L. Johnston and E. C. Kerr, THIS JOURNAL, **72**, 4733 (1950).

The entropy at 298.16°K. is 18.13 ± 0.03 e.u. of which 0.03 e.u. was contributed by the extrapolation below 15°K.

Acknowledgment.—We wish to acknowledge the assistance of Mr. W. D. Wood who assisted in the calculations.

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Catalytic Activity of Lanthanum and Strontium Manganite

BY G. PARRAVANO

RECEIVED JUNE 20, 1952

Recent work of Jonker and van Santen[1] and Volger[2] has shown that compounds of the general formula $(La_{1-\delta}Sr_\delta)(Mn^{+3}_{1-\delta}Mn^{+4}_\delta)O_3$ can be prepared from a mixture of the corresponding oxides or carbonates. Strontium up to $\delta = 0.7$ can be introduced in the $LaMnO_3$ phase without changing its perowskite structure. These compounds have a magnetic Curie temperature which is dependent on the amount of strontium added, and the temperature coefficient of the electrical resistivity shows anomalous behavior; it is positive for the ferromagnetic state and negative above the Curie point. It was therefore considered interesting to investigate the possibility of a relationship between the anomalous behavior of the temperature coefficient of the resistivity of these compounds and the activity of the solid surface to catalyze a chemical reaction. The compound $La_{0.65}Sr_{0.35}MnO_3$ was chosen for this investigation because it possesses the highest Curie point (~373°K.) of the series, and because it was found that at that temperature the oxidation of carbon monoxide on the above compound proceeded at rates which could be experimentally detected.

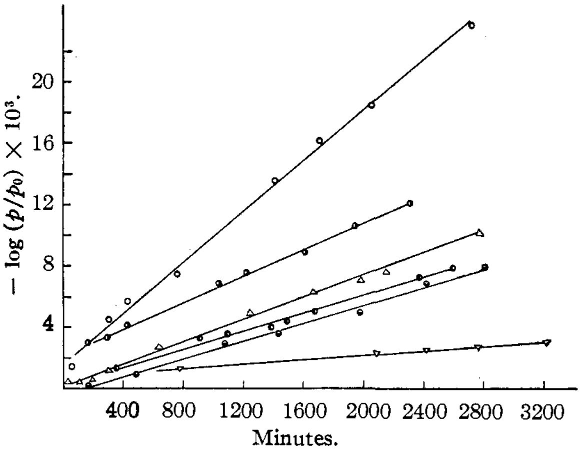

Fig. 1.—Oxidation of carbon monoxide on $La_{0.65}Sr_{0.35}MnO_3$ (2.139 g.): $CO/O_2 = 2/1$; $P_0 = 280$ mm.: ▽, 50°; ◐, 81.5°; ◒, 88°; △, 96°; ◑. 100°; ○. 105°.

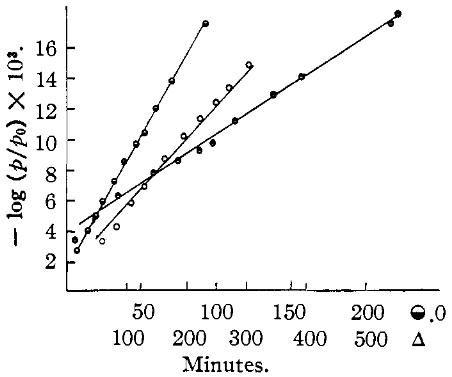

Fig. 2.—Oxidation of carbon monoxide on $La_{0.65}Sr_{0.35}MnO_3$ (2.139 g.): $CO/O_2 = 2/1$; $P_0 = 280$ mm.: △, 140°; ○, 183°; ◒. 212°.

$La_{0.65}Sr_{0.35}MnO_3$ was prepared by ball milling a mixture of stoichiometric amounts of C.P. manganese carbonate, strontium oxide and lanthanum oxalate for 1 hour. The mixture was then fired in a platinum crucible in air at 850° for 5 hours, milled again for 1 hour and finally heated at 900° for an additional 3 hours.

Purification of gases and apparatus used for the catalytic experiments have already been described.[3] It was found that the experimental data on the oxidation reaction could be fitted quite well to a first-order equation (Figs. 1, 2). Values for the velocity constant, k(min.$^{-1}$, g^{-1}), at different temperatures are presented in the following table and in Fig. 3, where they are plotted according to the Arrhenius equation, from which an over-all activation energy of 10.6 kcal./mole could be derived.

TABLE I

OXIDATION OF CARBON MONOXIDE ON $La_{0.65}Sr_{0.35}MnO_3$

$CO/O_2 = 2/1$, $p_0 = 280$ mm.

t, °C.	$k \times 10^6$, min.$^{-1}$, g^{-1}	t, °C.	$k \times 10^6$, min.$^{-1}$, g^{-1}
50	0.34	105	3.83
81.5	1.45	140	11.8
88	1.37	183	49.0
95	1.69	212	82.0
100	2.17		

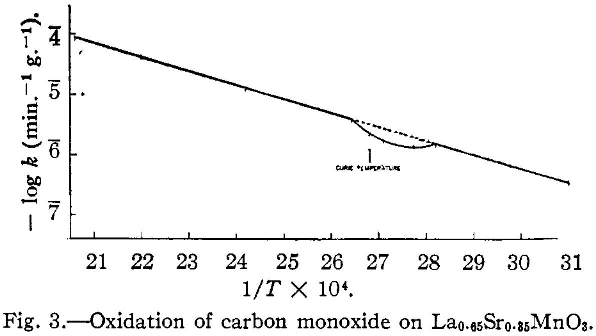

Fig. 3.—Oxidation of carbon monoxide on $La_{0.65}Sr_{0.35}MnO_3$. Arrhenius plot.

From the experimental data it is clear that the oxidation reaction shows the same activation energy below and above the Curie point of the catalyst. This is in disagreement with the magneto-catalytic effect studied by Hedvall.[4] According to this effect the temperature coefficient of the activity of a catalyst is markedly different below and above its

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[1] G. H. Jonker and J. H. van Santen, *Physica*, **16**, 337 (1950).

[2] "Semiconducting Materials," Butterworth Scientific Publications, London, 1951, Chapter by J. Volger.

[3] G. Parravano, THIS JOURNAL, **74**, 1448 (1952).

[4] For a review on this effect see: Schwab, "Handbuch der Katalyse," Vol. 6, Springer, Verlag Wien, 1943, chapter by J. A. Hedvall.

Curie point. In the present case, however, different magnetic states of the catalyst have no effect on the reaction. The same deduction can be drawn as to the reversal of the temperature coefficient of the resistivity of the catalyst. On the other hand, the data of Fig. 3 show that in the neighborhood of the ferromagnetic transition an anomaly is present in the rate of the catalytic reaction. This is in agreement with previous findings of Forestier and Lille,[5] who reported anomalies in the rate of the reaction $CO_2 + H_2 \rightleftarrows CO + H_2$ on Fe_3O_4, $SrFe_2O_4$, $NiFe_2O_4$ around the Curie temperature of the catalyst. The anomalous behavior of the activity of a catalytic reaction reported in the present communication is quite similar to that previously found for ferroelectric transitions occurring in sodium and potassium niobate and lanthanum ferrite.[6] It is interesting to note that the anomaly sets in somewhat below the Curie temperature. This could be explained by assuming that the ferromagnetic transition occurs on the surface at a lower temperature than in the bulk.

(5) H. Forestier and R. Lille, *Compt. rend.*, **204**, 265 (1937).

(6) G. Parravano, *J. Chem. Phys.*, **20**, 342 (1952).

FRICK CHEMICAL LABORATORY
PRINCETON, NEW JERSEY

Energy Relationships of Fused Ring Systems

BY WILLIAM S. JOHNSON

RECEIVED AUGUST 13, 1952

Using the Pitzer parameters[1] of 3.6 kcal. for the eclipsed, and 0.8 kcal. for the skew conformation (the staggered arrangement being set at zero) of the *n*-butane portion of a hydrocarbon chain, Turner[2] has calculated the difference in energy between the *cis* and *trans* forms of decalin to be 2.4 kcal., which, after correction for heats of vaporization, is in excellent agreement with the experimental observation. A simple method of carrying out the calculation of energy difference is as follows:

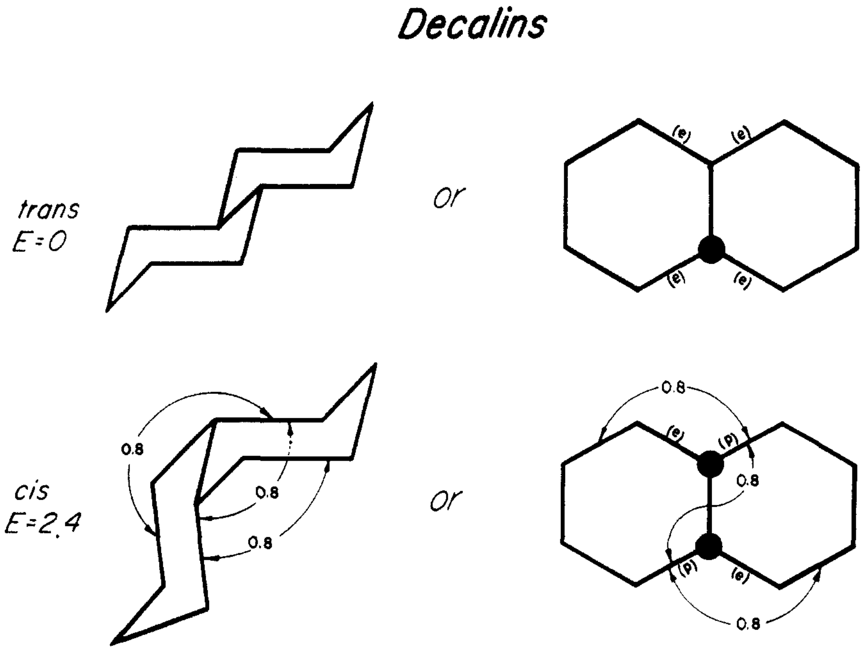

Fig. 1.

trans-Decalin is arbitrarily assigned the value zero; now *cis*-decalin differs from the *trans* isomer only in the three *skew* interactions involving the two polar (p) bonds as shown in Fig. 1. The energy difference, hence, is 3 × 0.8 = 2.4 kcal.

Applied to the perhydro-phenanthrenes and -anthracenes, this method of estimating energy differences leads to a more definitive picture of the relationships that were established qualitatively earlier,[3] and provides a criterion for establishing a more precise order of stability. In addition, this treatment affords an interrelation of the members of the phenanthrene and of the anthracene series on the same energy basis. It should be emphasized, however, that all of these energy differences are for the vapor phase at 25°, and small corrections would be expected[2] for the differences in heats of vaporization of the isomers.

The perhydroanthracenes (see Fig. 2) are conveniently considered first. Since the *trans–syn–trans* is the isomer of lowest energy, it is arbitrarily assigned the value zero. The *cis–syn–trans* form then differs from the *trans–syn–trans* by 3 *skew* interactions or 2.4 kcal. just as in the decalin series considered above. In the *cis–anti–cis* isomer an additional *cis*-decalin fusion is imposed which simply doubles the energy difference, *i.e.*, 6 *skew* interactions = 4.8 kcal.

The *trans–anti–trans* isomer differs from the *trans–syn–trans* in that the central ring assumes the boat conformation,[3] which accounts for a difference in energy of 5.6 kcal., namely, the difference between the chair and boat form of cyclohexane. In addition the *trans–anti–trans* form has two interactions (magnitude uncertain) of the type discussed by Turner,[4] which is defined by a rotation of 60° from the staggered conformation. The total energy difference for this isomer, hence, is a value somewhat greater than 5.6 kcal. In the *cis–syn–cis* isomer the situation is complicated by the fact that two of the (p) bonds appear in the unfavorable 1,3-relationship on the central cyclohexane ring. This interaction is comparable to that of the (p) (p) form of *cis*-1,3-dimethylcyclohexane for which Pitzer[1] has arbitrarily assigned the energy difference of 5.4 kcal. In the present case the interaction of two methylene groups is estimated to be about 8/9 (*skew* methylene/methyl) of this value or 4.8 kcal. With this

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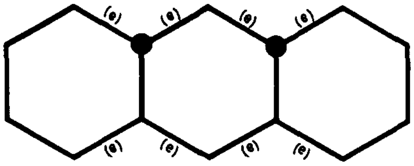
(1) (a) K. S. Pitzer, *Chem. Revs.*, **27**, 39 (1940); (b) C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

(2) R. B. Turner, *ibid.*, **74**, 2118 (1952).

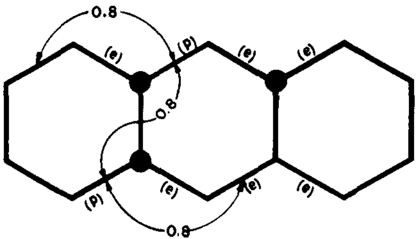
(3) W. S. Johnson, *Experientia*, **8**, 315 (1951).

(4) See formula IX, ref. 2.

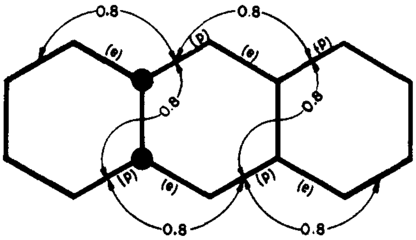
Perhydroanthracenes



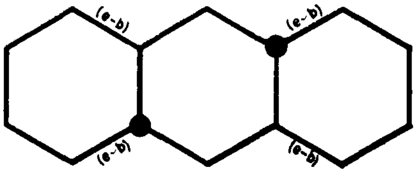
trans-syn-trans, E = 0 *kcal.*



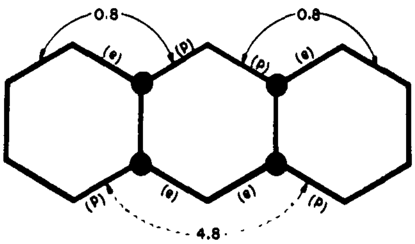
cis-syn-trans, E = 2.4 *kcal.*
(trans-anti-cis)



cis-anti-cis, E = 4.8 *kcal.*



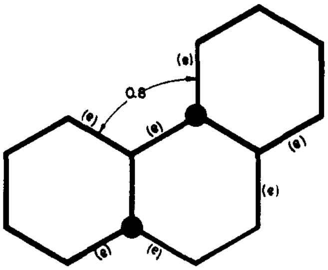
trans-anti-trans, E>5.6 *kcal.*



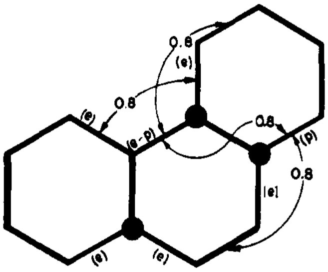
cis-syn-cis, E = ca. 6.4 *kcal.*

Fig. 2.

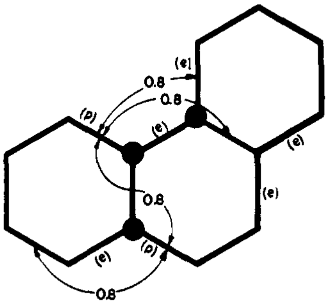
Perhydrophenanthrenes



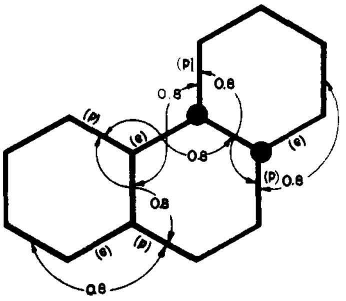
trans-anti-trans, E = 0.8 *kcal.*



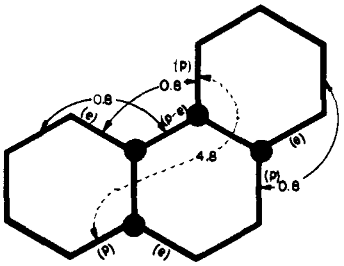
trans-anti-cis, E = 3.2 *kcal.*



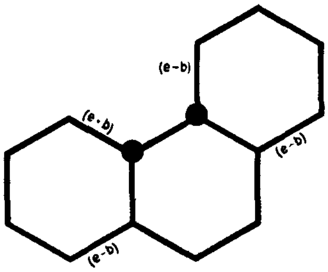
cis-syn-trans, E = 3.2 *kcal.*



cis-anti-cis, E = 4.8 *kcal.*



cis-syn-cis, E = ca. 7.2 *kcal.*



trans-syn-trans, E = >5.6 *kcal.*

Fig. 3.

parameter, the energy differences for the *cis–syn–cis* isomer becomes *ca.* 2 × 0.8 + 4.8 = 6.4 kcal.

The most stable of the perhydrophenanthrenes, the *trans–anti–trans* isomer, differs from the *trans–syn–trans* perhydroanthracene by one *skew* interaction between the bonds forming the angle of the three rings, or by 0.8 kcal. (see Fig. 3). The *trans–anti–cis* and *cis–syn–trans* isomers both have one additional *cis*-decalin interaction making the total energy difference 3.2 kcal. The case of the *cis–anti–cis* isomer is of particular interest since the earlier method of analysis[3] did not distinguish between the form with 1,2-(p) (p) substituents on the central cyclohexane ring (as shown in Fig. 3) and the form with 1,4-(p) (p) substituents (Fig. 4). In the former the angular skew interaction is eliminated, and the energy difference is defined simply by two *cis*-decalin interactions, or 4.8 kcal. just as in the *cis–anti–cis*-perhydroanthracene. In the latter conformation, the angular *skew* interaction is operative producing an 0.8 kcal. increment or a total difference of 5.6 kcal. The former conformation, therefore, is the more stable.

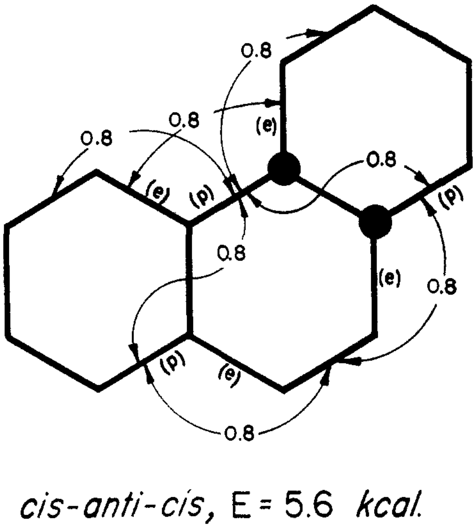


Fig. 4.

The *cis–syn–cis*-perhydrophenanthrene has a 1,3-(p) (p) interaction of the type considered above in the *cis–syn–cis*-perhydroanthracene. If the parameter 4.8 kcal. is invoked for this interaction the total energy difference becomes 7.2 kcal. It is difficult to estimate the energy difference of *trans–syn–trans*-perhydrophenanthrene. In addition to the boat conformation for the central ring,[3] the bonds forming the angle define an eclipsed conformation giving rise to an interaction of the type shown in Fig. 5. The contribution of this interaction is not easily evaluated; however, the total energy difference of the *trans–syn–trans* form should be greater than 5.6 kcal.

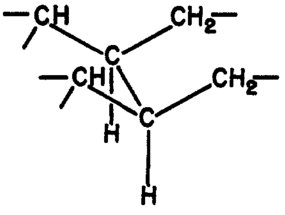


Fig. 5.

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The Chemistry of Aliphatic Phosphonic Acids. I. Alkylation of Methanediphosphonic Acid[1]

BY GENNADY M. KOSOLAPOFF

RECEIVED OCTOBER 30, 1952

Some time ago we reported a study of the alkylation at the central carbon atom of trialkyl phosphonoacetates, *i.e.*, compounds of the general type $(RO)_2P(O)CH_2CO_2R$.[2]

The phosphonoacetates can be regarded as partial phosphorus-bearing analogs of dialkyl malonates. The ready alkylation and dialkylation of the former showed very nicely the active methylene character of the central group in these esters, but the question still remained as to the source of the active methylene character, for this could have originated solely in the carboxylic end of the molecule.

In order to resolve this question we investigated the possibility of alkylation of tetraalkyl methanediphosphonates, *i.e.*, esters of the general type $(RO)_2P(O)CH_2P(O)(OR)_2$, which can be regarded as the true phosphorus analogs of the malonates. A few minor points relative to the preparation of the tetraethyl esters were clarified and it was established that esters higher than tetraethyl cannot be very satisfactory model substances, owing to very high boiling points. Since the purification of the reaction products centers exclusively in the fractionation procedures, the use of very high-boiling materials is undesirable. The sensitivity of the methyl esters to hydrolysis made such esters equally undesirable.

It was found that tetraethyl methanediphosphonate reacts readily with potassium in inert solvent, the reaction being quite exothermic. The resulting potassio derivative alkylates moderately readily with *n*-butyl bromide yielding the corresponding tetraethyl pentane-1,1-diphosphonate, which was characterized and hydrolyzed to the free acid which was also characterized. The rather unsatisfactory yields of the products effectively precluded the extension of the work to dialkylation reactions. However, the monoalkylation was demonstrated beyond doubt. The behavior of the mixture indicated that a considerable portion of the ester undergoing alkylation suffers ester-cleavage with subsequent formation of partial sodium salts. Such reactions have been noted for other esters of phosphonic acids[3] and present a serious problem to be solved in respect to satisfactory isolation of such substances.

The activity of the hydrogen in the methylene group of the diphosphonate can be attributed to

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[1] Presented at the Southeastern Regional Meeting. October, 1952.

[2] G. M. Kosolapoff and J. S. Powell, THIS JOURNAL, **72**, 4198 (1950). See the bibliography in this paper for earlier references.

[3] V. S. Abramov and M. N. Morozova, *Zhur. Obshchei Khim.*, **22**, 257 (1952).

one of the two possible causes. One of these can be the operation of the inductive effect of the two PO(OR)$_2$ groups attached to the methylene group. The other cause can be the partial double bond character of the P(O) linkage, which would permit the formation of an enolic structure involving the methylene group as well as the P(O) group, in a manner analogous to that customarily formulated for the sodio malonates and to which is usually attributed the stability and the ease of formation of such enolates. The very readiness of the reaction of the ester with potassium seems to argue for the latter explanation. Obviously if one assumes the completely semi-polar character of the P(O) linkages the formulation of the enol becomes impossible. Naturally, our observation is not the terminal solution of the true nature of the P(O) link, which has eluded such a solution after numerous experimental approaches.

The methylene activity in the diphosphonates has been made a starting point for further studies of alkylation of ordinary esters of aliphatic phosphonic acids, which coupled with a study of dipole moments of the compounds involved, may be expected to throw more light on the problem. The results of this work will be reported at a later date.

Experimental Part

Tetraethyl Methanediphosphonate.—This ester has been prepared earlier by Ford-Moore and Williams[4a] and by Schwarzenbach and Zurc.[4b] The method used by the former group was the most convenient for our purpose and the following description gives the details which were omitted by the previous workers in their synthesis in publication. Freshly distilled methylene iodide (103 g., b.p. 85–86° at 35 mm.) was rapidly added to 200 g. of triethyl phosphite (kindly supplied by the Virginia-Carolina Chemical Company; the product was redistilled before use) in a 500-ml. round-bottom flask, which was attached to a 16-inch Vigreux column. The mixture was heated rapidly to 160° by means of a pre-heated oil-bath. The colorless mixture acquired a dark brown-violet color which persisted for some 10 minutes, after which a vigorous reaction set in, with rapid evolution of ethyl iodide, which was collected in a cooled receiver. The reaction and the distillation were complete within 20 minutes, when the bath was heated to 170° for 10 minutes without causing any further change. Approximately 88 g. of ethyl iodide was collected for a 72.5% yield.

The reaction mixture was distilled under reduced pressure through a short fractionating column and gave, after redistillation, three fractions, as follows. The first fraction of 89 g. was composed in main of diethyl ethanephosphonate, b.p. up to 100° (mostly 98–100°) at 30 mm. The second fraction, which boiled at 95–135° at 0.5–0.4 mm. weighed 91 g. and was composed mainly (63 g.) of diethyl iodomethanephosphonate, b.p. 100° at 0.5 mm., 59% yield. The third fraction consisting of tetraethyl methanediphosphonate boiled at 135-137° at 0.4 mm. and weighed 20 g., for an 18% yield.

A somewhat smaller excess of triethyl phosphite (88 g. treated with 54 g. of methylene iodide) gave 31 g. of diethyl iodomethanephosphonate and 10 g. of tetraethyl methanediphosphonate. The large excess of the phosphite is quite essential for securing an appreciable yield of the disubstituted derivative.

Attempts to improve the yield of the latter by heating the isolated iodomethane derivative with triethyl phosphite were of dubious value, for the products were composed largely of diethyl ethanephosphonate and the iodomethane derivative, with only very small amounts of the diphosphonate. This result is in accord with the known sluggishness of the halogen in halomethanephosphonates. It also indicates that the Arbuzov–Michaelis reaction with dihalides essentially completes itself in the initial stage, at least with methylene iodide, and is not a true two-step reaction.

Alkylation of the Diphosphonate.—The diphosphonate (20 g.) was diluted with one volume of dry xylene and the solution was added over a 15-minute period to 2.7 g. of sliced potassium suspended in 250 ml. of dry xylene. The reaction evolved an appreciable amount of heat and resulted in an initial formation of a light flocculent precipitate which was largely dissipated after two hours required for completion of the reaction. The mixture was gently heated for the last few minutes to facilitate the reaction. (If the mixture is heated and the metal is kept in molten state, the addition of the diphosphonate causes a very vigorous reaction and the evolved gas causes severe foaming.)

The mixture was then treated with 20 g. (excess) of *n*-butyl bromide and was stirred for three hours without any visible change. The flask was then heated cautiously to the reflux temperature and the heating was continued for 3.5 hr. at which time a definite precipitate of potassium bromide formed. This was filtered off and the filtrate was fractionated, yielding 14 g. of unreacted ester and 5 g. of diethyl pentane-1,1-diphosphonate, a colorless viscous liquid, b.p. 147–149° at 0.3 mm., n^{20}_{D} 1.4428. This was hydrolyzed by refluxing overnight with 50 ml. of concentrated hydrochloric acid and evaporation to dryness with an infrared lamp. The product was recrystallized twice from water by repeated evaporation to remove any residual hydrochloric acid. The extremely hygroscopic pentane-1,1-diphosphonic acid was obtained in the form of waxy colorless needles which, after drying in high vacuum at 100°, soften at 143° and melt at 163–165°. The product gave a sharp depression of mixed melting point with methanediphosphonic acid.

Analytical.—The acid was titrated electrometrically to *p*H 5 according to Schwarzenbach.[4b] Calcd. for BuCH(PO$_3$H$_2$)$_2$: P, 26.7; equiv. wt., 116. Found: P, 26.5, 26.5; equiv. wt., 114, 114.5.

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(4) (a) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947); (b) G. Schwarzenbach and J. Zurc, *Monatsh.*, **81**, 202 (1950).

The Growth and Analysis of Barium Oxide Crystals Containing a Stoichiometric Excess of Barium[1]

BY GEORGE G. LIBOWITZ

RECEIVED OCTOBER 6, 1952

In studying the possible existence of a suboxide of barium, Schriel[2] obtained small crystallites of barium oxide by dissolving BaO in molten barium metal. These crystallites were colored deep red, and contained a stoichiometric excess of barium in the crystal lattice. Schriel's analysis of these crystals showed that they contained from 0.6 to 1.3% excess barium. As a result of the present work, these values were shown to be too high due to the presence of microscopic globules of free barium metal which were found embedded in these crystals. Because of the interest in barium oxide as a semiconductor, large crystals of this red barium oxide were desired, as well as an accurate method of determining the excess barium in the crystal lattice. By the method described below, crystals as large as 2 mm. thick by 1 cm.^{2} have been grown at this Laboratory.

Experimental

Growth of Barium Oxide Crystals.—A mixture of 60% barium metal chips and 40% barium oxide was put into a steel crucible, 1.25 in. in diameter and 4 in. long, so that only half the crucible was filled. The crucible was covered, and the lower half placed into a molybdenum wire wound furnace. The entire system was evacuated to a pressure of less than 10^{-4} mm. and heated at about 900° for 60–80

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(1) This work has been supported by the Office of Naval Research.

(2) M. Schriel, *Z. anorg. Chem.*, **231**, 313 (1937).

hours. The barium oxide first dissolved in the molten barium, and then as the barium evaporated and condensed at the top of the crucible, which was at a much lower temperature, a thick layer of red barium oxide formed at the surface of the solution. This layer consisted of a few large single crystals, and its thickness depended upon the amount of barium evaporated. The crystals were removed from the barium melt by dissolving the barium in a 2:1 toluene-absolute alcohol mixture. The function of the toluene was to retard the precipitation of barium ethylate. There was also a slight reaction between the barium oxide and the absolute alcohol[3]

$$BaO + 2C_2H_5OH \rightleftarrows Ba(C_2H_5O)_2 + H_2O$$

The water produced in this reaction causes a thin layer of barium hydroxide to be formed on the surface of the BaO crystals. However, this layer of hydroxide is easily removed by polishing the crystals.

Analysis of the Crystals.—In order to eliminate the error due to the occluded globules of barium metal mentioned above, the crystals were ground to a fine powder and washed with dry liquid ammonia, which dissolved the free barium metal without reacting with the barium oxide. The method used for the analysis was a modification of Berdennikowa's[4] method for oxide coated cathodes. The barium was placed into the sample tube of the apparatus shown in Fig. (1). After evacuating and outgassing the system, which has a total volume of 35 cc., the water in the liquid nitrogen trap was distilled into the sample tube. As the barium oxide dissolved, the excess barium reacted with the water to form hydrogen gas

$$Ba + 2H_2O \longrightarrow Ba(OH)_2 + H_2$$

After the barium oxide was completely dissolved, the water was recondensed in the liquid nitrogen trap, and the pressure of the hydrogen gas was measured with a thermocouple vacuum gage. The percentage of excess barium was calculated from the amount of hydrogen gas present. All the work on barium oxide was carried out either in a dry-box or in a water-free atmosphere.

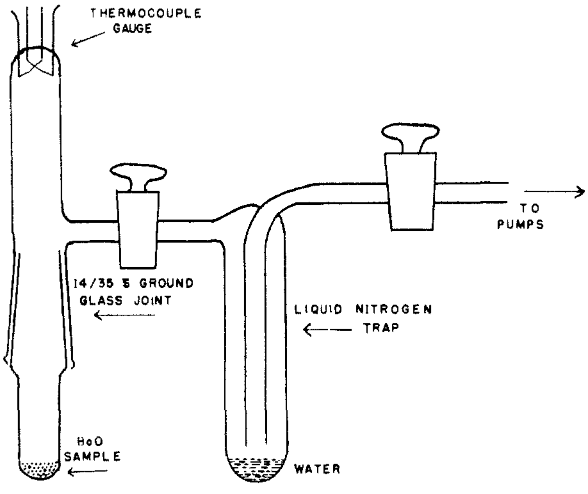

Fig. 1.

Discussion

Because the crystals were not perfectly homogeneous, the amount of barium in stoichiometric excess varied slightly from crystal to crystal within the same crystal growing run. Table I gives the percentages by weight of excess barium for two crystal growing runs. The three values given for run 48 represent three separate crystals taken from different sections of the surface layer of barium oxide.

TABLE I

Run no.	Time, hr.	Temp., °C.	Excess barium, %
35	60	890–910	0.14
48	73	880–905	.091
			.085
			.104

Optical absorption measurements taken on these crystals by Kane[5] indicate that the excess barium is not present as colloidal aggregates, as believed by Schriel, but either as interstitial barium atoms or as oxygen vacancies in the lattice. More recent investigations (to be published soon) at this Laboratory, however, indicate that the interpretation of Kane's experiment may be more complicated.

Acknowledgment.—The author wishes to thank Prof. R. L. Sproull for his advice.

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(3) G. F. Smith, *Ind. Eng. Chem., Anal. Ed.*, **1**, 72 (1929).

(4) T. P. Berdennikowa, *Physik. Z. Sowjetunion*, **2**, 77 (1932).

(5) E. O. Kane, *J. Applied Phys.*, **22**, 1214 (1951).

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A Study of the Periodate Method for Determining End-group Values[1]

BY M. MORRISON, A. C. KUYPER AND J. M. ORTEN

RECEIVED SEPTEMBER 24, 1952

The use of periodate for the determination of the degree of branching of certain carbohydrate substances such as starch and glycogen is based on its reaction with those monosaccharide units which contain alcohol groups on three adjacent carbon atoms and the resultant formation of a molecule of formic acid. Since in these polymers only the terminal glucose units have this necessary configuration, the amount of formic acid produced becomes a measure of the average length of the glucose chains, or of the degree of branching of these substances.

Many modifications of the periodate method have been proposed. These differ in the conditions of the oxidation reaction and in the method used for the determination of the formic acid. Formic acid has been determined after separation by steam distillation from the reaction mixture[2] and also iodometrically[3,4] but it is usually titrated directly with alkali after excess periodate is removed by reaction with ethylene glycol. The procedures employing direct titration variously specify that for quantitative recovery of formic acid, titration must be performed with different indicators to end-points of about pH 5.5,[4,5] pH 6.0,[6] pH 8.0,[7] and pH 8.2.[8] However, the titration curve of pure formic acid shows that it is quantitatively titrated at any of these pH values and that the choice of end-point should have little, if any, influence on the quantitative titration. The different modifications appear to give widely different end-group values. In this

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[1] This paper is taken from a dissertation presented by M. Morrison in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, Wayne University, 1952. The investigation was supported by a grant from the Griffith Laboratories, Chicago.

(2) Y. Khouvine and G. Arragon, *Bull. soc. chim.*, **8**, 676 (1941).

(3) M. Abdel-Akher and F. Smith, THIS JOURNAL, **73**, 994 (1951).

(4) T. G. Halsall, E. K. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 1427 (1947).

(5) A. L. Potter and W. Z. Hassid, THIS JOURNAL, **70**, 3488 (1948).

(6) M. Schlamowitz, *J. Biol. Chem.*, **188**, 145 (1951).

(7) K. H. Meyer and P. Rathgeb, *Helv. Chim. Acta*, **31**, 1540 (1948).

(8) A. Jeanes and C. A. Wilham, THIS JOURNAL, **72**, 2655 (1950).

Laboratory the method of Potter and Hassid[5] when applied to maltose, the sugar recommended for standardization, did not give the theoretical yield of 3 moles of formic acid. Furthermore, a fading end-point suggested that something other than free formic acid was included in the titration.

In order to study the reaction further, and to determine to what extent substances other than formic acid are titrated in the periodate method, potentiometric titration curves of the various reaction mixtures were prepared (Figs. 1, 2 and 3) and these were compared with the theoretical titration curves of the formic acid present in these mixtures. The experimental titration curves were corrected for the accumulated hydrogen and hydroxyl ions and for the titration of the iodate and small amounts of silicate in the reaction mixtures. The theoretical titration curve for the formic acid present in each titration mixture was calculated on the basis of a *pK'* for formic acid of 3.56, as determined by separate titration under the same experimental conditions, and of the amount of substance titrated within one or two *p*H units[9] of this value. At *p*H values below about 4.2 these calculated curves coincide with the experimentally determined curves (Figs. 1, 2 and 3). This indicates that over this region formic acid, or acids having the same dissociation constant as formic acid, are being titrated.[10]

At *p*H values higher than 4.2 the titration curve of the reaction products of periodate and maltose (Fig. 1) does not coincide with the theoretical titration curve for formic acid. In addition, there is a drift of *p*H values obtained in the titration after each addition of alkali from a relatively high value to a lower *p*H value (indicated by the double line in the figure). When periodate acts on maltose in the pyranose form it may be shown that, of the three molecules of formic acid produced, one is liberated as an ester. Meyer and Rathgab[7] reported the formation of a similar ester in the periodate oxidation of lactose. Hydrolysis of the ester by alkali and the liberation of formic acid would account for the additional titration and the fading end-point. The amount of formic acid produced as measured by the theoretical titration curve corresponds to about 2.5 moles per mole of maltose. This probably includes formic acid produced by partial hydrolysis of the ester. A titration corresponding to the theoretical 3 moles of formic acid is obtained only at relatively high *p*H values where the ester is more completely hydrolyzed and where other groups are also included in the titration.

The experimentally determined titration curve of the substances formed in the reaction between periodate and sucrose (Fig. 2) corresponds closely to the calculated curve of formic acid over the *p*H range below 6.5, indicating that formic acid alone, or acids having the same dissociation constant, are being titrated.[10] The curve differs from that of the maltose reaction mixture in that it is almost vertical over the *p*H range of 5.0 to 6.5 and shows a smaller amount of drift of *p*H in alkaline solution. This drift in *p*H cannot be attributed to the hydrolysis

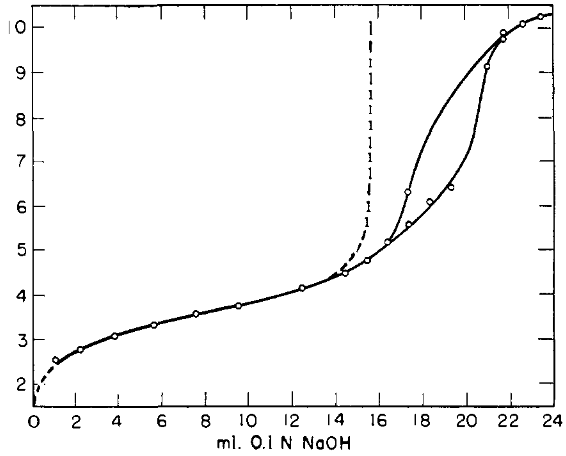

Fig. 1.—Potentiometric titration curve of periodate-maltose reaction mixture: —, experimental curve, the double line indicates a drift in *p*H; ----, theoretical curve of the formic acid present in the reaction mixture.

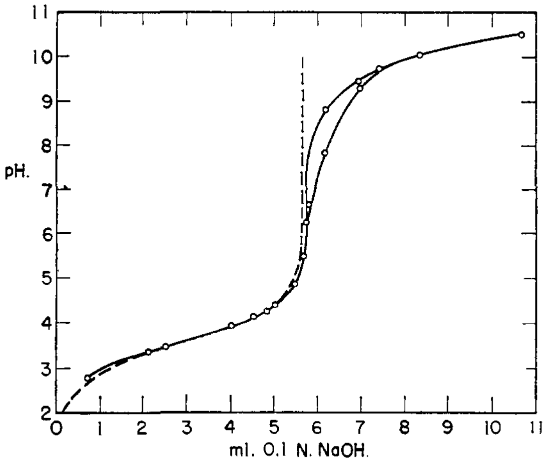

Fig. 2.—Potentiometric titration curve of periodate-sucrose reaction mixture: —, experimental curve, the double line indicates a drift in *p*H; ----, theoretical curve of the formic acid present in the reaction mixture.

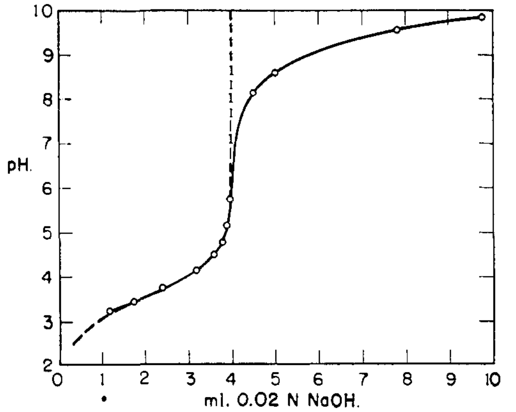

Fig. 3.—Potentiometric titration curve of periodate-glycogen reaction mixture: —, experimental curve: ----, theoretical curve of formic acid present in the reaction mixture.

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[9] D. D. Van Slyke, *J. Biol. Chem.*, **52**, 525 (1922).

[10] Lactic and oxalic acids have dissociation constants within a few tenths of a *pK* unit of formic acid and cannot be readily distinguished on the basis of their titration curves. Failure to form an insoluble calcium salt indicated the absence of oxalic acid.

of an ester, similar to that found in the periodate–maltose reaction mixture. The reaction mixture was made acid with hydrochloric acid and again titrated. The titration curve showed the presence of an increased amount of organic acid corresponding to that liberated during the former titration. The curve was again almost identical with that of an acid of pK' 3.56.

The amount of free formic acid determined in the first titration of the periodate–sucrose reaction mixture to pH 6.0 corresponds to 80–90% of the theoretical value, one mole per mole of sucrose, and depends on the time allowed for the oxidation reaction (Figs. 2, 4). Titration to about pH 8.0 as performed by others[7,8] includes products liberated during the titration and may give a value which indicates a theoretical yield. However, the end-point at this pH is not definite and other groups are included in the titration. When formic acid was added to and incubated with a periodate oxidation mixture, it was quantitatively recovered from the mixture, indicating that this substance is not oxidized by the periodate. The amount of periodate utilized in the reaction remained about constant after 45 hours and corresponded to the theoretical amount of 3 moles per mole of sucrose oxidized. The inclusion of 20 ml. of 0.1 M formic acid in periodate–sucrose or in periodate–glycogen reaction mixtures did not increase the amounts of formic acid liberated during titration in alkaline solution.

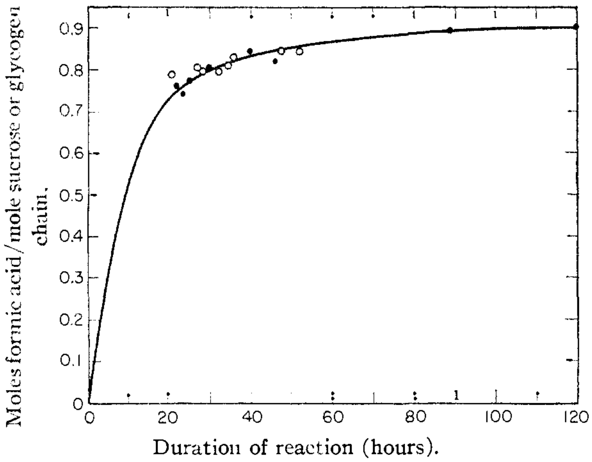

Fig. 4.—Time study of periodate reaction: ●, with sucrose; O, with glycogen.

The titration curve of the reaction mixture of periodate with glycogen (Fig. 3) is similar to that with sucrose except for the presence of much less formic acid and a smaller drift in the alkaline range (not shown in the figure) of only a few hundredths of a pH unit, which is of uncertain significance. Unidentified groups are titrated beginning in the neighborhood of pH 7.0.

The use of the periodate reaction for the determination of end-group values of polysaccharides requires that the conditions of the reaction be standardized on the basis of reaction with a carbohydrate of known composition, and that the reaction occurs in the same manner with this reference substance, as with the polysaccharide. For use as this reference substance, sucrose appears to be preferred to maltose because, like polysaccharides, it is not reducing and because titration of the reaction mixture to pH 6.0 gives a definite, non-fading end-point. The amount of free formic acid produced in the reaction, however, depends on the time allowed for the reaction and amounts to only 80 or 90% of the theoretical value. In applying the reaction to polysaccharides it appears that the most reasonable procedure is to assume the same percentage production of formic acid and to allow a corresponding correction. Support of this procedure is found in the similarity in the rates of reaction (Fig. 4) and the shapes of the titration curves of the reaction products of these two substances (Figs. 2, 3), and also in results obtained by other workers[7,8] who found it necessary to titrate periodate reaction mixtures to high pH values and include substances other than formic acid in order to obtain the theoretical titration value. When a correction was applied, end-group values obtained by the periodate method were in substantial agreement with those obtained by Cori and Larner by an enzymatic method[11] when both methods were run on the same carbohydrate samples.[12]

In view of the foregoing observations, a modified procedure was devised, as outlined under "Experimental." The oxidation was allowed to proceed for 30 hours, and the reaction mixture was titrated with brom cresol purple to pH 6.0. The formic acid measured in this titration was corrected for an average 81% yield as determined with sucrose and the end-group value, or average chain length, was calculated from this corrected figure. End-group values, determined on ten different glycogen samples in this way varied from 12.4 to 14.5 glucose units per end-group.[13]

Experimental

Periodate Oxidation.—0.222 g. of carbohydrate (either sucrose, maltose, arrowroot starch or glycogen) was dissolved in 10 ml. of 3% sodium chloride in a 50-ml. erlenmeyer flask. The flask was placed in a deep-freeze at −10° until a slush formed and then 10 ml. of 0.37 M sodium metaperiodate at room temperature was added and the solution was placed in the refrigerator at 2°. After 30 hours or other desired time interval, the solution was removed from the refrigerator and 2 ml. of ethylene glycol was added. The solution was then kept at room temperature in a dark place for at least half an hour before it was titrated.

Titration of Reaction Mixture.—The reaction mixture was titrated in a CO_2-free atmosphere with CO_2-free sodium hydroxide either with brom cresol purple to pH 6.0, or potentiometrically, using a glass electrode. For potentiometric titration, the reaction mixture was adjusted to 0.4 ionic strength and titrated with sodium hydroxide in a 0.4 M solution of sodium chloride. The titration curves were corrected for the accumulation of hydrogen and hydroxyl ions, for the titration of iodate formed during the oxidation and for small amounts of silicate dissolved from the glassware. The pK' of formic acid was determined from a titration curve of pure formic acid in the presence of the same salt concentration used in the experimental samples.

Periodate consumption was determined by the method of Fleury and Lange as described by Jackson.[14]

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[11] G. T. Cori and J. Larner, *J. Biol. Chem.*, **188**, 17 (1951).

[12] Samples of two polysaccharides were kindly supplied by Dr. G. Cori.

[13] Unpublished experiments.

[14] E. L. Jackson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944.

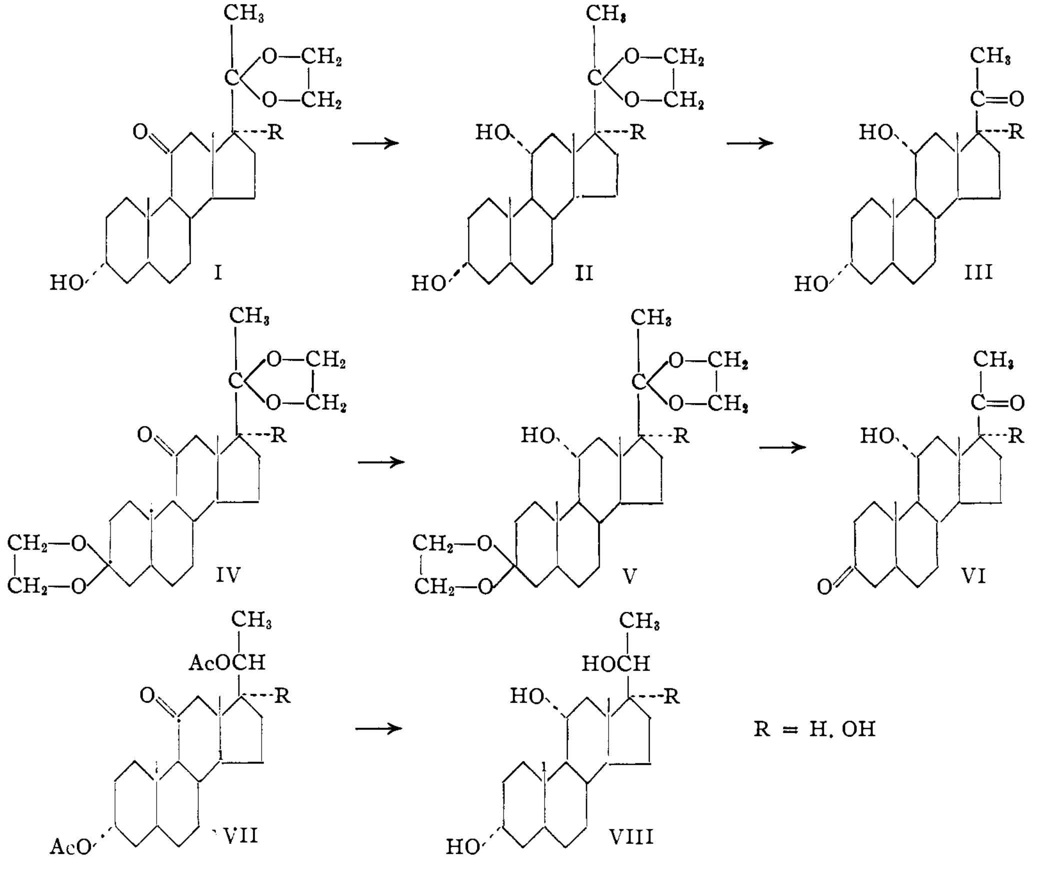
11-Oxygenated Steroids. V. The Preparation of 11α-Hydroxypregnanes[1]

BY EUGENE P. OLIVETO, HERSHEL L. HERZOG AND E. B. HERSHBERG

RECEIVED NOVEMBER 14, 1952

The recent discovery[2] that 11-ketosteroids can be reduced to the corresponding 11α-hydroxysteroids in excellent yield by means of sodium in boiling 1-propanol has led to a simple and convenient method for the preparation of 11α-hydroxypregnanes, most of which have been prepared for the first time.

The appropriate pregnan-11,20-dione or -3,11,20-trione was converted to the 20-ethylene ketal (I) or 3,20-bis-ethylene ketal (IV) by means of ethylene glycol.[3] Sodium in refluxing propanol converted the free 11-ketone to an 11α-hydroxyl in excellent yield, and hydrolysis of the ketals with dilute mineral acid[2c] or aqueous acetic acid[3] generated the 11α-hydroxy ketones (III and VI):



An alternate method for preparing the 3,20-diketo-11α-hydroxypregnanes made use of the relative inertness[2a,2c] of the 11α-hydroxyl group toward mild oxidizing agents. Thus, N-bromoacetamide oxidation of pregnan-3α,11α-diol-20-one (III, R = H) and pregnan-3α,11α,17α-triol-20-one (III, R = OH) produced the corresponding 3-ketones (VI) in good yield.

Pregnan-3α,20β-diol-11-one 3,20-diacetate (VII, R = H) and pregnan-3α,17α,20β-triol-11-one 3,20-diacetate[1] (VII, R = OH) were both reduced by sodium and 1-propanol to the free 3α,11α,20β-triol (VIII, R = H) and 3α,11α,17α,20β-tetrol (VIII, R = OH), respectively.

Experimental[4]

The preparation of pregnan-3α-ol-11,20-dione 20-ethylene ketal, pregnan-3α,17α-diol-11,20-dione 20-ethylene ketal, pregnan-3,11,20-trione 3,20-bis-ethylene ketal, pregnan-17α-ol-3,11,20-trione 3,20-bis-ethylene ketal, pregnan-3α,20β-diol-11-one diacetate and pregnan-3α,17α,20β-triol-11-one, 3,20-diacetate has been reported previously.[1,3]

The sodium reduction was carried out by dissolving the steroid in approximately 50 volumes of *n*-propyl alcohol, heating the solution to reflux, and adding 5 times the weight of sodium as rapidly as possible. Refluxing was continued for 0.5 hour whereupon an equal volume of methanol was added. When all the sodium had reacted, about 0.5 the volume of water was added, and then steam introduced to distil off the alcohols. The reduced dioxolanes precipitated and after removal by filtration, were crystallized from the appropriate solvents.

The ketal groups were split off by hot aqueous acetic acid[3] or by acetone and dilute hydrochloric acid.[2c]

N-Bromoacetamide oxidations of pregnan-3α,11α-diol-20-one and pregnan-3α,11α,17α-triol-20-one were carried out in the usual manner[2c] in aqueous acetone for two hours in the ice-box. Yields were 85–90%.

In one case, the intermediate V (R = H) was difficult to crystallize, so that pregnan-3,11,20-trione 3,20-bis-ethylene

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(1) Part IV, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **75**, 488 (1953).

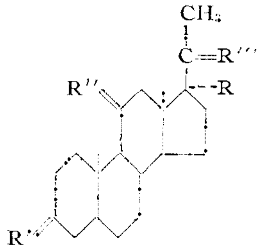
(2) (a) Hershel L. Herzog, Eugene P. Oliveto, Margaret A. Jevnik and E. B. Hershberg, *ibid.*, **74**, 4470 (1952); (b) H. Heusser, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952); (c) Hershel L. Herzog, Margaret A. Jevnik and E. B. Hershberg, THIS JOURNAL, **75**, 269 (1953).

(3) Eugene P. Oliveto, Temple Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953).

(4) All m.ps. are corrected. All rotations were taken in a one decimeter tube at a concentration of about 1%. We are indebted to Mr. Edwin Conner, Mrs. Alice Barella, Mrs. Beatrice Grebe, Mrs. Elizabeth McEntire and Miss Joan Mustachio for the analytical and rotational data.

TABLE I

PHYSICAL CONSTANTS AND YIELD DATA



R′	R″	R‴	Yield, %	M.p., °C.	[α]D	Empirical formula	Anal. Carbon, % Calcd.	Anal. Carbon, % Found	Anal. Hydrogen, % Calcd.	Anal. Hydrogen, % Found	Recrystallization solvent
	R = H										
OH H	OH H	O—CH$_2$ O—CH$_2$	97	199.0–199.8	+19.8°	$C_{23}H_{38}O_4$	72.97	72.86	10.12	10.41	Acetone–hexane
OH H	OH H	O	90	181.4–182.4	+89.4	$C_{21}H_{34}O_3$	75.40	75.19	10.25	10.29	Acetone–hexane
OAc H	OAc H	O	..	147.0–148.0	+74.3[a]	$C_{25}H_{38}O_5$	71.74	71.95	9.15	9.40	Ether–hexane
OH H	OH H	OHβ H	92	186.5–187.8	− 9.9[b]	$C_{21}H_{36}O_3$	74.94	74.75	10.78	11.02	Acetone
OAc H	OAc H	OAcβ H	..	259–262	+25.2[b]	$C_{27}H_{42}O_6$	70.10	70.15	9.15	9.36	Acetone
O—CH$_2$ O—CH$_2$	OH H	O—CH$_2$ O—CH$_2$	Not isolated								
O	OH H	O	89	108.0–110.0[c]	+89.0	$C_{21}H_{32}O_3$	75.86	76.05	9.70	10.05	Hexane
O	OAc H	O	..	149.4–150.8[d]	+51.8	$C_{23}H_{34}O_4$	73.76	73.59	9.15	8.96	Hexane
	R = OH										
OH H	OH H	O—CH$_2$ O—CH$_2$	97	213.2–214.0	−13.3	$C_{23}H_{38}O_5$	70.01	69.70	9.71	9.74	Methanol–water
OH H	OH H	O	94	Solvated	+25.8	$C_{21}H_{34}O_4 \cdot H_2O$	68.44	68.14	9.85	10.07	Acetone–water
OAc H	OAc H	O	..	190.2–191.4	+21.7	$C_{25}H_{38}O_6$	69.09	68.80	8.81	9.09	Acetone–water
OH H	OH H	OHβ H	90	238–241	−19.7[b]	$C_{21}H_{36}O_4$	71.55	71.34	10.29	10.24	Methanol–water

TABLE I (*Continued*)

R′	R″	R‴	Yield, %	M.p., °C.	$[\alpha]_D$	Empirical formula	Anal. Carbon, % Calcd.	Anal. Carbon, % Found	Anal. Hodrogen, % Calcd.	Anal. Hodrogen, % Found	Recrystallization solvent
	R = H										
OAc H	OAc H	OAcβ H	..	277–278	+ 5.2[a]	$C_{27}H_{42}O_7$	67.75	68.06	8.85	9.04	Methanol
O—CH₂ O—CH₂	OH H	O—CH₂ O—CH₂	98	109.5–111.5	−10.8	$C_{25}H_{40}O_6$	68.77	68.42	9.24	9.50	Acetone–hexane
O	OH H	O	92	192.6–194.0	+21.3	$C_{21}H_{32}O_4$	72.38	72.62	9.26	9.49	Acetone–water
O	OAc H	O	..	204.4–206.2	− 1.4	$C_{23}H_{34}O_5$	70.74	70.95	8.78	8.85	Acetone–water

All rotations are in acetone, except those noted.
[a] Chloroform. [b] Dioxane. [c] Reported m.p. 116–118°, $[\alpha]_D$ +91° ($CHCl_3$) [O. Mancera, A. Zaffaroni, B. Rubin, F. Sondheimer, G. Rosenkrantz and C. Djerassi, THIS JOURNAL, 4, 3711 (1952)]; m.p. 102–105°, $[\alpha]_D$ +83° ($CHCl_3$) [H. Murray and D. Peterson, U. S. 2,602,769]. [d] Reported m.p. 148–149°, $[\alpha]_D$ +65° ($CHCl_3$) [Djerassi, *et al.*, ref. *c*].

ketal (IV, R = H) was converted to pregnan-11α-ol-3,20-dione (VI, R = H) without isolation of pregnan-11α-ol-3,20-dione 3,20-bis-ethylene ketal (V, R = H).

Acetates were prepared by the usual procedure with acetic anhydride and pyridine.

Physical constants and yield data are recorded in Table I.

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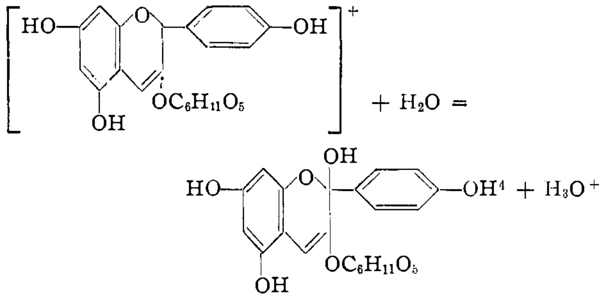
On the Relation between Spectral Changes and pH of the Anthocyanin Pelargonidin 3-Monoglucoside[1]

BY ERNEST SONDHEIMER

RECEIVED NOVEMBER 7, 1952

The predominant effect of increasing hydrogen ion activity on the spectral properties of pelargonidin 3-monoglucoside is an increase in the intensity of absorption in the visible region.[2] Furthermore, on the addition of water to unbuffered benzopyrylium salt solutions a decrease in the light absorption in the visible range is observed which is greater than can be accounted for merely by dilution effects. These observations can be explained by the hypothesis that there is an equilibrium between hydronium ions, a red modification R^+ and a colorless form ROH of the anthocyanin. Evidence for this view is presented below. The method used here has previously been applied to many acid–base indicators but not to anthocyanins.[3]

The hydrolysis reaction may be shown as



then

$$pK = \log \frac{R^+}{ROH} + pH$$

In Table I the effects of changes in the pH on the light absorption at 500 millimicrons and on the pK values are shown. For the pH range in which the R^+ concentration varies between 98.4 and 10.8% the pK is constant within the experimental error. Thus one of the conditions necessary to consider this as an equilibrium reaction has been met. This evidence is strengthened by the observations that the pK is independent of the anthocyanin concentration and that the equilibrium may be approached from either side. The isolation of color-

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[1] Journal Article No. 908. New York State Agricultural Experiment Station.

[2] E. Sondheimer and Z. I. Kertesz, THIS JOURNAL, **70**, 3476 (1948).

[3] I. M. Kolthoff "Acid–Base Indicators," translated by Ch. Rosenblum, The Macmillan Co., New York, N. Y., 1937.

[4] Although the pseudo-base is here represented as a 2-chromenol it is not known whether this is the predominant tautomer. J. A. Berson, THIS JOURNAL, **74**, 358 (1952), has shown that with some triphenylpyrylium pseudo-bases the open-chain 1,5-diketone was the only tautomer whose presence could be demonstrated.

less pseudo-bases on hydrolysis of several benzopyrylium salts by previous investigators[5] also supports the above results.

TABLE I

THE EQUILIBRIUM BETWEEN HYDRONIUM IONS, AND THE BENZOPYRYLIUM SALT AND THE PSEUDO-BASE OF PELARGONIDIN 3-MONOGLUCOSIDE AT 25°

*p*H	Optical density at 500 mμ	R^+, %	*pK*
1.18	1.075	98.4	2.99
1.42	1.050	96.2	2.82
1.74	1.025	93.7	2.92
1.99	0.980	89.7	2.93
2.16	.928	85.0	2.91
2.49	.855	78.3	3.05
2.58	.775	71.0	2.97
2.77	.665	60.9	2.96
3.08	.490	44.9	2.99
3.36	.338	30.9	3.01
3.62	.227	20.8	3.04
3.83	.159	14.6	3.06
4.01	.118	10.8	3.09
		Av. *pK*	2.98 ± 0.06

The anthocyanin was isolated from strawberries by a previously described method.[2] It was purified by recrystallizing the picrate six times and then converted to the chloride. The values in Table I were obtained with a 4.27×10^{-5} molar anthocyanin solution in Sörensen's disodium citrate–hydrochloric acid buffers. Measurements were taken at 500 mμ with a Beckman spectrophotometer, model C, using 1 cm. Corex cells, at least one hour after the solutions had been prepared. The *p*H values were determined with a Beckman *p*H meter, model G. All measurements were made at 25°.

(5) P. Karrer and C. Trugenberger, *Helv. Chim. Acta*, **28**, 444 (1945); I. M. Heilbron and A. Zaki, *J. Chem. Soc.*, 1902 (1926); D. W. Hill and R. R. Melhuish, *ibid.*, 1161 (1935).

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A New Synthesis of Oxindole

BY ALEXANDER B. NEILL

RECEIVED OCTOBER 25, 1952

While evaluating known[1,2] and potential methods for preparing oxindole, it was found that the synthesis used by Meyer and Beer[3] to prepare 3,4-dihydrocarbostyril from 2-chlorodihydrocinnamic acid could also be used for the synthesis of oxindole. The method consisted of heating *o*-chlorophenylacetic acid with concentrated ammonium hydroxide and copper powder in a sealed tube at 155–165° for eight hours whereupon cyclization to form oxindole took place.

Experimental

***o*-Chlorobenzyl cyanide** was prepared in a 91–94% yield from *o*-chlorobenzyl chloride by a method similar to that given in "Organic Syntheses" for the preparation of benzyl cyanide.[4]

***o*-Chlorophenylacetic acid** was prepared in an 85–88% yield from *o*-chlorobenzyl cyanide by a method similar to that given in "Organic Syntheses" for the preparation of phenylacetic acid.[5]

Oxindole.—The best yields of oxindole were obtained by using the following conditions. A mixture of 5.3 g. (0.031 mole) of *o*-chlorophenylacetic acid, 0.56 g. of copper powder or 1.0 g. of cupric acetate and 28 ml. of concd. ammonium hydroxide was heated in a sealed pressure tube at 155–165° for 8 hours in a Carius oven. After allowing the tube to come to room temperature in the oven, the tube was opened, and the crystals which formed were filtered, dissolved in hot water and treated with Darco. On cooling, the white crystals which formed were filtered and dried. A yield of 1.4 to 1.8 g. (34 to 43%) of oxindole melting at 126–127° was obtained. A mixed melting point of this compound with an authentic sample of oxindole prepared by the method of Di Carlo[6] showed no depression.

(1) See W. C. Sumpter, *Chem. Revs.*, **37**, 443 (1945), for a review of the methods for preparing oxindole.

(2) At the time that this work was begun the method by which R. Stolle and R. Bergdoll, *J. prakt. Chem.*, **128**, 1 (1930), cyclized α-chloroacetanilide with aluminium chloride was found to be unsuccessful. Subsequently the work of S. Sugassawa, I. Satoda and J. Yanagisawa, *J. Pharm. Soc. Japan*, **58**, 139 (In English 29) (1938), showed that a ratio of 1.8 parts of aluminum chloride to one part of α-choloroacetanilide was necessary for the reaction instead of a ratio of one to one as reported by Stolle and Bergdoll. Similar results have been reported recently by P. L. Julian in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 144.

(3) H. Meyer and R. Beer, *Monatsh.*, **34**, 1179 (1913).

(4) R. Adams and A. F. Thal, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 107.

(5) Reference 4, p. 437, note 3.

(6) F. J. Di Carlo, THIS JOURNAL, **66**, 1420 (1944).

DIVISION OF CHEMISTRY
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Urea–Formaldehyde Kinetic Studies. IV. Reactions of Methylenebisureas

BY LLOYD E. SMYTHE

RECEIVED AUGUST 11, 1952

In the course of studies of the reaction of dilute solutions of urea and simple N-alkylureas with formaldehyde at *p*H 7.15 it was observed that certain methylenebisureas once formed, showed no sign of hydrolysis, further condensation or polymerization.[1] Methylene compounds have been postulated as important units in urea–formaldehyde plastics and it was desirable that the reactions of methylenebisureas be studied further. It was found that the polarographic method of analysis used previously[1] was more suitable for this study than titration methods. The use of titration methods for the estimation of formaldehyde when working with more concentrated solutions must receive careful consideration, since condensation products have been shown to influence the estimation.[2] Preliminary studies have indicated that methylol compounds,[2] methylenebisureas and more highly condensed systems each have separately different effects on the usual titration methods. Consequently, the study of later stages of condensation in more concentrated solution must await reliable analytical methods. Borzee and Smetz[3] have recently used titration methods in a study of condensation reactions of urea and formaldehyde in concentrated solution but do not state whether errors were introduced by the condensation products.

The present work concerning the formation[1] and reactions of methylenebisureas requires further

(1) L. E. Smythe, THIS JOURNAL, **75**, 574 (1953).

(2) L. E. Smythe, *J. Phys. Colloid Chem.*, **51**, 396 (1947).

investigation since, owing to the dilution of reactants and close control of conditions, it is not possible to isolate ureas from the reaction mixture. The identification of such ureas depends mainly on melting point determinations and analysis after concentration of the solution and crystallization of the products. A difficulty is that if dilute solutions were concentrated at any stage in the reaction, the products might not be those formed originally. At present, there do not appear to be suitable methods available for the identification of ureas in dilute solution.

Experimental

The apparatus and general technique used in this study has been described.[3] Compounds prepared were: monomethylolurea, $NH_2CONHCH_2OH$, m.p. 111°, Einhorn and Hamburger[4]; methylenebisurea, $NH_2CONHCH_2NHCONH_2$, m.p. 218° decomp., Kadowaki[5]; methylenebismethylurea, $CH_3NHCONHCH_2NHCONHCH_3$, m.p. 184°, Kadowaki[5]; methylenebisethylurea, $C_2H_5NHCONHCH_2NHCONHC_2H_5$, m.p. 117°, Einhorn[6]; monomethylolmethylenebisethylurea, $C_2H_5NHCON(CH_2OH)CH_2NHCONHC_2H_5$, m.p. 171°, Einhorn.[6] It was found necessary to modify several of the above methods of preparation where hydrochloric acid was used as condensing agent. Where the solutions were allowed to develop excessive heat during the initial reaction, ill-defined products of indefinite melting point were obtained. These would not respond to purification.

The stability of methylenebisureas in dilute solution (Sørensen buffer[1]) was tested as follows: 0.1 M solutions of the compounds listed above were prepared with the buffer. The solutions were allowed to stand in sealed tubes at temperatures of 25° and 35°. No free formaldehyde was detected by polarographic analysis at any time up to three weeks.

The reaction of methylenebisureas with formaldehyde was also studied. 0.2 M solutions of the compounds listed above, prepared with Sørensen buffer,[1] were allowed to react with equal volumes of 0.2 M solutions of formaldehyde in the same buffer at temperatures of 25° and 35°. For periods of up to three weeks the concentration of free formaldehyde remained unaltered at 0.1 M.

Methylenebisureas were found to be unstable in the presence of a strong base. In this case, lithium hydroxide was selected as the base, since it would provide for comparison of the results with those of Crowe and Lynch.[7] Equal volumes of 0.2 M solutions of the compounds listed above and 0.1 N LiOH reacted together at 25° with the results given in Table I. The decompositions were first order from zero time. Products of the reaction are probably the parent urea and formaldehyde,[7] identification of the urea in dilute solution being difficult.

TABLE I

Urea	CH_2O liberated	CH_2O liberated, %	$k \times 10^3$ sec.$^{-1}$
$NH_2CONHCH_2OH$	Rapid	85[a]	1.40
$NH_2CONHCH_2NHCONH_2$	Slow	75	0.08
$CH_3NHCONHCH_2NHCONHCH_3$	Slow	70	.06
$C_2H_5NHCONHCH_2NHCONHC_2H_5$	Slow	70	.07
$C_2H_5NHCON(CH_2OH)CH_2NHCONHC_2H_5$	Rapid	87[b]	.60

[a] After 60 minutes. [b] After 140 minutes refers to 87% of the CH_2O available from the methylol group; CH_2O from the methylene group being liberated slowly thereafter.

Discussion

Previous work has shown[1] that when simple N-alkyl substituted ureas react with formaldehyde in dilute neutral solution, methylenebisureas may be the principal reaction products. Methylenebisureas would not react with additional formaldehyde and this has been discussed in terms of the state of urea and formaldehyde in dilute neutral solutions.[1]

Crowe and Lynch[7] have shown that increasing hydroxyl ion concentration results in higher rate constants by shift of both urea and formaldehyde activation equilibria. It was also not possible to calculate the observed effect of change in reaction rate with pH.

While de Jong[8] claims a linear relationship between reaction rate and hydrogen or hydroxyl ion concentration in the pH range 2–11, no such relationship was observed for the decomposition of methylenebisureas at pH 12.7 (0.5 N LiOH) and for some other concentrations of lithium hydroxide, for which data are not presented.

Both Crowe and Lynch[7] and the author[1] have found the accuracy of the polarographic method for following the concentration of unreacted formaldehyde to be ±3–5% of the value determined and it seems clear that this method offers considerable advantages over titration methods such as the iodometric.[9] Investigations have shown that the iodometric method gives accurate results only when applied to pure formaldehyde solutions,[9] yet de Jong[8] gives titration figures accurate to ±0.01 ml. with 0.1 N iodine. It is doubtful if such accuracy can be obtained by any volumetric method for the estimation of free CH_2O in the presence of reaction products.

The methylenebisureas were found to be stable in neutral solution[1] and unstable in alkaline solution, being hydrolyzed to the original urea and formaldehyde (Table I). Base catalysis appears to be involved and a study of the decompositions under a variety of conditions would be desirable.

It was found that methylol groups are more easily hydrolyzed than methylene linkages (Table I). The value of k for the hydrolysis of monomethylolurea is close to that obtained by Crowe and Lynch[7] and was included for purposes of comparison. In neutral solution it is seen that formaldehyde will not react with methylenebisethylurea to form monomethylolmethylenebisethylurea owing to hydration of the urea and lack of a strongly nucleophilic nitrogen center. However, if the monomethylolmethylenebisethylurea be formed separately under more drastic conditions[6] the methylol group is seen to be easily hydrolyzed under alkaline conditions, the remaining methylene link being then slowly attacked.

Borzee and Smets[3] have observed that with equimolar concentrated neutral solutions of monomethylolurea and formaldehyde, beyond an initial slow reaction, the course and rate of the reaction is essentially the same as for urea and formaldehyde. This was explained on the basis that the condensation of monomethylolurea itself with formaldehyde comprises the initial slow reaction and that the over-all velocity is increased by a more rapid reaction between monomethylolurea and one of the hydrolysis products of this, urea itself. Studies in

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[3] A. Borzee and G. Smets, *J. Polymer Sci.*, **8**, 371 (1952).

[4] A. Einhorn and A. Hamburger, *Ber.*, **41**, 24 (1908).

[5] H. Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936).

[6] A. Einhorn, *Ann.*, **361**, 113 (1908).

[7] G. A. Crowe and C. C. Lynch, THIS JOURNAL, **70**, 3795 (1948).

[8] J. I. de Jong, *Recueil*, **71**, 643 (1952); **71**, 661 (1952); **71**, 890 (1952).

[9] J. Walker, "Formaldehyde," A. C. S. Monograph 98, 1944, p. 260.

dilute neutral solution however suggest that hydrolysis of monomethylolurea is negligible and under such conditions it is unlikely that the nucleophilic nitrogen of urea would attack any but an electrophilic center of monomethylolurea, if such a center existed. This latter point awaits clarification by further studies of the reactions of methylolureas.

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The Condensation of Kojic Acid with Crotonic Acid and with β-Bromopropionic Acid[1]

BY L. L. WOODS

RECEIVED OCTOBER 18, 1952

Kojic acid reacts with crotonic acid in the presence of sodium bicarbonate to give a new acid, probably the 2-methyl-2-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-propionic acid, but possibly 1-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-butyric acid. The evidence for condensation at the 6-position of kojic acid lies in the fact that the 2- and 5-positions in the product are available for acetylation.

The reaction of kojic acid with β-bromopropionic acid gives 2-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-propionic acid, a product previously obtained by the cyanoethylation of kojic acid.[2]

Experimental[3]

Reaction of Crotonic Acid with Kojic Acid.—One hundred ml. of absolute ethanol, 8.6 g. of crotonic acid and 8.4 g. of sodium bicarbonate were thoroughly agitated and warmed, after which 14.2 g. of kojic acid was added. The mixture was then refluxed for 20 hours, acidified with concentrated hydrochloric acid and filtered while warm. Evaporation of the filtrate to about 50 ml., followed by chilling the solution, gave 14.4 g. of a solid. This solid was recrystallized twice from absolute ethanol and once from benzene (in which it is only slightly soluble), giving white prisms which melt at 154.5° and give a red coloration with ferric chloride solution.

Anal. Calcd. for $C_{10}H_{12}O_6$: C, 52.61; H, 5.26. Found: C, 52.40; H, 5.04.

The above product and acetic anhydride gave an ester which was crystallized from ethanol and benzene. The ester separates as pale-yellow rosettes melting at 133–135°.

Anal. Calcd. for $C_{14}H_{16}O_8$: C. 53.87; H. 5.12. Found: C. 53.44; H, 4.89.

The high melting point of the ester suggests that the product of the condensation of crotonic acid with kojic acid may be 1-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-butyric acid, rather than 2-methyl-2-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-propionic acid.

The *p*-bromophenacyl bromide derivative, prepared as was the corresponding derivative of 2-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-propionic acid[2] and recrystallized from absolute ethanol and benzene, separated as white crystals melting at 182.5°.

Anal. Calcd. for $C_{18}H_{17}O_7Br$: C, 50.82; H. 4.00. Found: C, 50.49; H, 3.88.

Reaction of β-Bromopropionic Acid with Kojic Acid.—A mixture of 14.2 g. of kojic acid, 15.3 g. of β-bromopropionic acid and 8.4 g. of sodium bicarbonate in 100 ml. of absolute ethanol was refluxed for five hours, acidified with 4 ml. of concentrated hydrochloric acid, and filtered while hot. Evaporation of the filtrate to dryness on the steam-bath gave 25 g. of a waxy product. Twelve grams of pale yellow crystals, melting at 146–147°, were obtained from the waxy solid by solution in 50 ml. of boiling absolute ethanol, addition of 70 ml. of hot ethyl acetate, treatment with Norite, filtration and cooling of the filtrate. Three more crystallizations from absolute ethanol gave white crystals melting at 152°. The product gives a deep red coloration with ferric chloride solution.

Anal. Calcd. for $C_9H_{10}O_6$: C. 50.46; H, 4.67. Found: C. 50.78; H, 4.82.

The product gives the same *p*-bromophenacyl bromide and acetic anhydride derivative as were obtained from 2-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-propionic acid,[2] thus proving the identity of the compound.

Treatment of the product with thionyl chloride in ligroin gave a dark solid which was crystallized from hot water, giving yellow-orange needles. Sublimation produced white needles, melting at 164.5° and giving a red coloration with ferric chloride solution.

Anal. Calcd. for $C_9H_9O_5Cl$: C. 46.45; H, 3.87. Found: C, 46.09; H, 3.64.

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[1] The author wishes to express his thanks to the Research Corporation for a grant-in-aid on this research. The kojic acid used in these experiments was furnished through the courtesy of the Corn Products Company.

[2] L. L. Woods, THIS JOURNAL, **74**, 3959 (1952).

[3] All analyses were performed by Dr. Carl Tiedcke. Melting points were determined on a Fisher-Johns melting point assembly.

Some Ketonic Derivatives of Triaminoguanidine

BY F. L. SCOTT, M. CASHMAN AND J. REILLY

RECEIVED SEPTEMBER 9, 1952

We have recently[1] reported the reactions between triaminoguanidine nitrate and some aldehydes. This present communication extends these observations to ketonic derivatives. The most reactive ketones prove to be the 2-acetylthiophene and 3-acetylthionaphthene. Alloxan, benzylideneacetone, benzoin, cyclohexanone, acetophenone and isatin reacted fairly readily. Reactions between the triaminoguanidine salt and benzophenone, *m*-aminoacetophenone, *m*-cyanoacetophenone, chalcone and dibenzalacetone were slow. The cyclohexanone derivative was isolated as its picrate.

Methyl isopropyl ketone, methyl nonyl ketone, methyl ethyl ketone, methyl heptyl ketone, benzylidenebenzyl phenyl ketone, methyl benzyl ketone all failed to react—triaminoguanidine being recovered unchanged in yields of from 95–100%. Both acetone and β-ionone did react, but the nitrates and picrates of the derivatives were sticky solids and have proved difficult to purify. Hydroquinone was the main reaction product of the vigorous interaction of triaminoguanidine and *p*-benzoquinone. With β-naphthoquinone reaction again was brisk, this time, however, with the formation of black tars.

Experimental[2,3]

The hydrazones were formed by refluxing triaminoguanidine (1 mole) with the ketone (3 moles) in aqueous ethanolic solutions. A few drops of nitric acid were used as catalyst.

1,1-Bis-(3,5-dimethyl-1-pyrazolyl)-4-methyl-2,3-diazahepta-1,3-diene-6-one.—To 1.6 g. of triaminoguanidine nitrate dissolved in 100 ml. of water was added 3 ml. of acetylacetone. The mixture was well agitated, adopted a slight yellow tint, and on standing globules of a greenish-yellow oil separated. These then slowly crystallized, were filtered off and recrystallized from ethanol; yield 64–70%. These

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[1] F. L. Scott, M. Cashman and J. Reilly, THIS JOURNAL, **74**, 5802 (1952).

[2] All m.ps. have been taken with short stem Anschütz thermometers.

[3] All analyses are by Drs. Weiler and Strauss, Oxford.

TABLE I

KETONIC HYDRAZONES OF TRIAMINOGUANIDINE

Ketone	Yield,[a] %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Acetylthiophene	98	217	$C_{19}H_{20}S_3N_6$[b]	53.27	53.14	4.67	4.75[c]
3-Acetylthionaphthalene	93	283	$C_{31}H_{26}S_3N_6$[b]	64.35	64.49	4.50	4.53[d]
Alloxan	94	>300	$C_{13}H_{14}N_{12}O_{12}$[e,f]	29.43	29.3	2.64	2.58
Benzylideneacetone	72	125	$C_{31}H_{35}N_7O_4$[g,h]	65.3	65.85	6.16	6.44
Benzoin	97	190	$C_{43}H_{43}N_7O_8$[g,j]	65.73	65.52	5.47	5.0
Chalcone	75	132	$C_{46}H_{39}N_7O_3$[g]	74.9	74.76	5.29	5.39
Cyclohexanone	56.5	135	$C_{19}H_{27}N_9O$[g,k,l]	45.41	45.44	5.57	5.62
Dibenzylacetone	95	227	$C_{52}H_{44}N_6$[g]	83.0	83.0	5.85	5.87
m-Cyanoacetophenone	95	237	$C_{28}H_{23}N_9$[b]	69.28	69.47	4.74	5.0

[a] All yields of crude material. [b] Recrystallized from pyridine and therefore tabulated data are those for the hydrazone free base. [c] Calcd. S, 22.43; found S, 22.49. [d] Calcd. S, 16.61; found S, 16.55. [e] Not recrystallized because of insolubility. [f] This formula is for a trihydrate. [g] Recrystallized from 95% alcohol. [h] This formula is for a monohydrate. [j] This formula is for a dihydrate. [k] Dihydrazone isolated as a picrate. [l] Yellow plates analyzing for 0.5 mole of water of crystallization.

crystals of the dipyrazolemonohydrazone, named above, were almost insoluble in ether, soluble in water and in alcohol. The nitron[4] test proved the absence of nitrate. *Anal.* Calcd. for $C_{16}H_{22}N_6O$: C, 61.1; H, 7.0; N, 26.75. Found: C, 60.8; H, 7.1; N, 26.7.

When the experiment was repeated, under reflux, for half an hour and the product precipitated by pouring into water, a 48% yield of a yellow amorphous powder, which after recrystallization from aqueous ethanol melted at 148° was obtained. Its nature is unknown. Its analysis suggested it to be of empirical formula $C_3H_4N_2$ and it did not form a picrate. *Anal.* Calcd. for $C_3H_4N_2$: C, 52.9; H, 5.8; N, 41.2. Found: C, 52.8; H, 5.7; N, 42.2.

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(4) *Cf.* J. E. Heck, H. Hunt and M. G. Mellon, *Analyst*, **59**, 18 (1934).

COMMUNICATIONS TO THE EDITOR

ENZYMATIC DEGRADATION OF THE CHOLESTEROL SIDE CHAIN IN CELL-FREE PREPARATIONS

Sir:

It has been demonstrated by Bloch, *et al.*,[1] that cholesterol can be converted to cholic acid in intact animals. These earlier studies have recently been extended by Chaikoff and his co-workers[2,3,4] who showed, in both animals and in surviving tissue slices, that the oxidation of the side chain proceeded at a relatively rapid rate while the cyclopentenophenanthrene nucleus was essentially inert. To facilitate a systematic study of the enzyme-catalyzed steps in this oxidation, we have obtained an active cell-free system from mouse liver tissue and report some of its properties below.

Mouse liver mitochondria were prepared by the method of Kielley and Kielley.[5] These preparations were unable to oxidize the C^{26}-carbon atom of 26-C^{14} labeled cholesterol[6] (added as a serum albumin stabilized emulsion) to CO_2, either alone or when supplemented with DPN, nicotinamide, adenylic acid, cytochrome C, magnesium ions and malate. The original sucrose homogenate, on the other hand, oxidized as much as 1.0% of the labeled carbon atom under the incubation conditions described in Table I. Microsome free supernatants, prepared

TABLE I

CHARACTERISTICS OF THE CHOLESTEROL OXIDASE SYSTEM

Individual flasks incubated in air at 37° contained one or more of the following components as indicated: 1.6 cc.[a] washed mitochondria in 0.25 *M* sucrose, M_w: 2.0 cc. homogenate-free of cell-debris and nuclei; 2.0 cc. microsome and mitochondria-free supernatant, S. Other additions were made to each flask unless otherwise indicated, at the following final concentrations: DPN, 0.0005 *M;* AMP, 0.002 *M;* nicotinamide, 0.02 *M.* The final volumes were made to 6.0 cc. with 1:1 0.9% KCl–0.2 *M* potassium phosphate buffer, *p*H 7.4; CO_2 was trapped in the center well in KOH and counted[7] as $BaCO_3$; 0.9 cc. 26-C^{14}-cholesterol was added as a 1% serum albumin stabilized emulsion containing 0.4 mg. cholesterol (42,000 c.p.m.[7])/cc. of saline-phosphate.

Expt.	Time of incubation, min.	Addition	Total c.p.m. in $BaCO_3$
I-1	120	Homogenate	206
2	33	M_w + S	8
3	63	M_w + S	43
4	120	M_w + S	197
5	120	M_w + dialyzed S	157
6	120	M_w + boiled, 3×concentrated S	0
7	120	M_w + S (no AMP)	124
8	120	M_w + S (0.22 cc. cholesterol emulsion)	96
II-1	120	M_w + S (stored at 3° for 24 hr.)	54
2	120	M_w + S (no DPN)	7
3	120	M_w + S (no DPN: TPN 0.0005 *M*)	2

[a] Equivalent to homogenate volume in flask 1.

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(1) K. Bloch, B. N. Berg and D. Rittenberg, *J. Biol Chem.*, **149**, 511 (1943).

(2) I. L. Chaikoff, *et al.*, *ibid.*, **194**, 413 (1952).

(3) M. D. Siperstein and I. L. Chaikoff, *ibid.*, **198**, 93 (1952).

(4) J. R. Meier, M. D. Siperstein and I. L. Chaikoff, *ibid.*, **198**, 105 (1952).

(5) W. W. Kielley and R. K. Kielley, *ibid.*, **191**, 485 (1951).

(6) A. I. Ryer, W. H. Gebert and N. M. Murrill, THIS JOURNAL, **72**, 4247 (1950).

(7) C. V. Robinson, *Science*, **112**, 198 (1950).