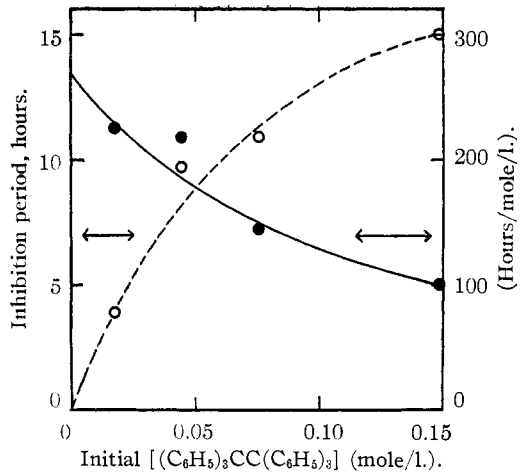

Fig. 2.—Inhibition periods in the polymerization of styrene, in hours (broken line), and in hours per unit concentration of hexaphenylethane (solid line).

This result may be due to the disappearance of hexaphenylethane in a side reaction, such as the addition to styrene; the addition of tri-biphenylmethyl to styrene to give a 2:1 product has been observed.[7] However, since our data are not consistent enough to permit analysis of the kinetics, the inhibition period per unit concentration of inhibitor has been plotted against the concentration of inhibitor in Fig. 2 and extrapolated to estimated zero concentration of inhibitor. Making the reasonable assumption that this extrapolation minimizes complications due to side reactions which consume hexaphenylethane, the results show that the induction period is of the order of two-hundred-forty to three-hundred hours per mole of substituted ethane initially present. Thus, such a solution would consume about 1/270 or 0.0037 mole of hexaphenylethane per hour. Normally, $5.32 \times 10^{-8} \times 905 = 4.8 \times 10^{-5}$ mole of polymer per liter per hour would have been produced. Hence, about 77 molecules of hexaphenylethane disappear (at zero ethane concentration) for each molecule of polystyrene that would have been formed in its absence. It follows that triphenylmethyl radicals must start nearly as many chains as they stop. The addition of hexa-arylethanes to double bonds seems to be the result of an initiation of "polymerization" by free radicals, and an even more effective termination by the same kind of radicals or by undissociated ethane, so that only *very* low molecular weight polymer is formed while triarylmethyl radicals, or undissociated ethane, remain.

We consider that this work leads to the following conclusions: Any free radical may start or terminate the polymerization of a styrene chain. Neither benzoquinone nor hexaphenylethane is suitable for measuring the spontaneous rate of chain initiation, nor for calculating its activation energy. Whether a source of free radicals will behave as a catalyst or an inhibitor depends on the balance between the rate of addition of these radicals to monomer, the rate of interaction of radicals and the rate of growth of the polymer radicals at the chosen temperature. If the radicals do not add rapidly or if they are supplied too fast, then a high radical concentration results and chain growth is restricted. If the radicals add very rapidly, or are supplied slowly enough, polymerization will result. These statements mean simply that the dividing line between catalysts and inhibitors is not clear cut; the differences between them are quantitative rather than qualitative.

(7) Marvel, Dec and Corner, THIS JOURNAL, **67**, 1855 (1945).

GENERAL LABORATORIES
UNITED STATES RUBBER COMPANY
PASSAIC, NEW JERSEY RECEIVED SEPTEMBER 12, 1947

The Periodate Oxidation of Some Dihydroxyaminoalkanes[1]

BY J. F. MEAD AND E. A. BARTRON

It has been reported previously[2] that two of the contiguously substituted dihydroxyaminoalkanes and possibly dihydrosphingosine[3] can be partially identified by the periodate or lead tetraacetate oxidation of the N-acetyl derivatives with measurement of the amount of oxidizing agent consumed.

A simpler method applicable to a wide variety of related compounds is the periodate oxidation[4] of the amino glycols themselves, with isolation of at least two of the oxidation products.

The reactions of the various types of isomeric compounds with periodate can be represented as follows

Type I $R—CHNH_2—CHOH—CH_2OH + 2IO_4^- \longrightarrow R—CHO + HCOOH + HCHO + NH_3 + 2IO_3^-$

Type II $R—CHOH—CHNH_2—CH_2OH + 2IO_4^- \longrightarrow R—CHO + HCONH_2 + HCHO + 2IO_3^-$

Type III $R—CHOH—CHOH—CH_2NH_2 + 2IO_4^- \longrightarrow R—CHO + HCOOH + HCHO + NH_3 + 2IO_3^-$

Type IV $CH_2OH—C(R)NH_2—CH_2OH + 2IO_4^- \longrightarrow R—CONH_2 + 2HCHO + 2IO_3^-$

Type V $CH_2OH—C(R)OH—CH_2NH_2 + 2IO_4^- \longrightarrow R—COOH + HCHO + NH_3 + 2IO_3^-$

It will be noticed that if R is different from H (as in the case of sphingosine) all five types give different products except I and III, which can be distinguished by oxidation of the N-acetyl derivatives[2] and measurement of the amount of formaldehyde produced.

In testing the method, the simplest substrates were used, and the products isolated or identified were those most easily isolated or determined quantitatively. As can be seen from Table I, the

(1) This work was supported by grant No. 840 (Penrose Fund) of the American Philosophical Society.

(2) C. Niemann, A. A. Benson and J. F. Mead, *J. Org. Chem.*, **8**, 397 (1943).

(3) After completion of this note a paper appeared by Carter, Glick, Norris and Phillips, *J. Biol. Chem.*, **170**, 1 (1947), who oxidized dihydrosphingosine to obtain formaldehyde, formic acid and ammonia.

(4) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1944, Chap. 8, p. 341.

method is both qualitative and quantitative. The yields, which in some cases would be greater than 100% if calculation were made on the basis of substrate actually oxidized can be explained by the differences in temperature of the oxidizing solutions resulting from the addition of the dimethyldihydroresorcinol in hot water (see below). Only one serious difficulty was experienced. In the cases in which both ammonia and formaldehyde were produced, only small yields of either could be obtained because of the formation of hexamethylenetetramine. This difficulty was partially overcome in the case of formaldehyde by an earlier addition of dimethyldihydroresorcinol, with which the formaldehyde apparently reacts preferentially. The compounds used for the reactions were selected because of availability and as examples of each type of product. Formaldehyde was isolated in each case, while acid or ammonia were titrated if the theoretical equation required their formation. If the equation and a qualitative test (for ammonia)[5] indicated the formation of an amide (II and IV), the solution was treated under hydrolytic conditions, and the acid formed was distilled and titrated.

TABLE I

Compound	% oxidized	% of theoretical amount of products isolated (based on substrate taken) HCHO	NH_3	HCOOH	CH_3COOH
$CH_2OH—CHOH—CH_2OH$	94.2	91.7		93.7	
$CH_2OH—CH_2NH_2$	84.4	69.2	59.0		
$CH_2OH—C(CH_3)NH_2—CH_3$	88.0	91.2	84.0		
$CH_2OH—C(CH_3)NH_2—CH_2OH$	89.2	92.6			73.5
$CH_2OH—CHOH—CH_2NH_2$	82.2	82.1		90.8	

Experimental

Determination of Completeness of Oxidation.—The substrate, about 10^{-4} mole, in water solution or emulsion was treated with a 10% excess over the theoretical amount of a saturated solution of potassium metaperiodate (1.66×10^{-2} mole per liter) for twenty minutes. To the resulting solution was added borax-boric acid buffer solution, and potassium iodide, and the liberated iodine was titrated with standard arsenite solution.

Determination of Formaldehyde.—In the absence of ammonia, the oxidation mixture, after standing for twenty minutes, was treated with a 10% excess over the theoretical amount of dimethyldihydroresorcinol[6] in alcohol solution, brought to *p*H 4, warmed to 60°, and allowed to stand in the ice-box until precipitation was complete. The formaldehyde dimethone was collected and weighed, and the melting point taken to determine the purity of the sample.

In case ammonia was formed in the reaction, the following procedure was adopted. The substrate and periodate solutions were mixed, and dimethyldihydroresorcinol in hot water solution was added after about three minutes. After twenty minutes, the solution was brought to *p*H 4 and treated as before.

Determination of Acid.—If no ammonia was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard alkali. If ammonia was formed, the solution was acidified with sulfuric acid and about three-fourths of it distilled. Water was added, and the distillation repeated. The distillate was then titrated with standard alkali.

(5) J. A. Sanchez, *Anales asoc. quim. argentina*, **24**, 366 (1926).

(6) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

Determination of Ammonia.—If no acid was formed in the reaction, the oxidation mixture, after twenty minutes, was titrated with standard acid.

Determination of Amides.—If the formation of amide was indicated (see above), the solution, after completion of the oxidation, was made strongly acidic with sulfuric acid, refluxed for two hours and then distilled to about one-fourth volume. Water was added, and the solution was again distilled to one-fourth volume, and the distillate titrated with standard alkali. If the acid formed was known, it was necessary to distill and titrate only 10% of the solution, and calculate the total amount originally present.[7]

(7) L. J. Gillespie and E. H. Walters, THIS JOURNAL, **39**, 2027 (1917).

CHEMICAL LABORATORY
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LOS ANGELES, CALIF. RECEIVED SEPTEMBER 24, 1947

Crystalline Procaine Penicillins

BY CHARLES J. SALIVAR, F. HOWARD HEDGER AND ELLIS V. BROWN

There is an urgent need for a penicillin dosage form which will give prolonged penicillin blood levels with more certainty and without the objectionable features of the currently available preparations.

We have prepared procaine salts of two penicillins and have milled them in vegetable oil to give injectable mixtures. Preliminary animal and clinical trials have indicated that significant and prolonged penicillin blood levels are obtainable with these preparations. These data will be published later.

For the preparation of procaine benzylpenicillin, 10 g. of sodium benzylpenicillin dissolved in 10 ml. of water is treated with a solution of 7.6 g. of procaine hydrochloride in 10 ml. of water and the reaction product is allowed to crystallize slowly. After crystallization is completed, the product is filtered, washed with water and dried in a vacuum drier at 50°.

The practically colorless crystalline procaine salt of benzylpenicillin melts (capillary) at 129–130°. *Anal.* Calcd. for $C_{29}H_{38}N_4O_6S \cdot H_2O$: N, 9.52; S, 5.44. Found: N, 9.78; S, 5.35.

The biological potency obtained by the Oxford plate method[1] against *S. aureus* is 1020 U./mg. The potency as determined iodometrically[2] is 1007 U./mg. The calculated value based on 1667 U./mg. for sodium benzylpenicillin is 1008 U./mg. The optical rotation is $[\alpha]^{25}D$ +173° (1% in 50% aqueous acetone).

Procaine *n*-amylpenicillin was also prepared in the same manner from sodium *n*-amylpenicillin.[3] It melts at 113–115°. *Anal.* Calcd. for $C_{27}H_{42}N_4O_6S \cdot H_2O$: N, 9.86; S, 5.63. Found: N, 9.79; S, 5.97.

(1) W. H. Schmidt and A. J. Moyer, *J. Bact.*, **47**, 199 (1944).

(2) J. F. Alicino, *Ind. Eng. Chem., Anal. Ed.*, **18**, 619 (1946).

(3) Report presented by C. J. Salivar, V. V. Bogert and E. V. Brown at the Conference on Antibiotic Research held in Washington, D. C., January 31, 1947, under the auspices of the Antibiotics Study Section of the National Institute of Health.