potential to yield HgSR and the anodic current CB is equal to CA. Similarly, at a potential D the actual current DG is equal to the difference between the hypothetical cathodic current DE and the anodic current DF. At the potential I the cysteine no longer yields an anodic current and the experimental current IH now corresponds to the true reduction current of cystine. The same, of course, is true at potentials more negative than I, and the experimental curve HK is also the true reduction wave. In conclusion it may be mentioned that potentials of the cystine-cysteine system measured with the dropping mercury electrode do not correspond to the thermodynamically reversible potentials of the system $\text{RSSR} + 2\text{H}^+ + 2e \rightleftarrows 2\text{RSH}$ but represent typical "mixed potentials."

Summary

1. Cystine may be determined polarographically at a *p*H of 1 using thymol to suppress the maximum. The diffusion current was found to be proportional to the concentration.

2. The diffusion coefficient of cystine was calculated to be 5.3×10^{-6} sq. cm./sec. in 0.1 *N* hydrochloric acid at 25°.

3. An analysis of the current-voltage curves shows that the reduction of cystine at the dropping electrode does not occur reversibly according to the reaction $\text{RSSR} + 2\text{H}^+ 2e \rightleftarrows 2\text{RSH}$, although the effect of *p*H upon the potential is given approximately by this equation.

4. Capillary active substances such as thymol, camphor, gelatin and methylene blue markedly shift the reduction curves of cystine to more negative potentials. It is proposed that this is caused by their inhibiting the orientation or adsorption of cystine at the surface of the mercury drop.

5. The first step in the waves obtained with cystine in buffer solutions with a *p*H between 3 and 9.2 is explained by the fact that the cysteine formed by reduction reacts anodically with mercury with the formation of mercurous cysteinate. The first step of the wave does not correspond to the true reduction wave of cystine, while the second step does represent the true reduction wave. The potential of cystine-cysteine solutions at the dropping electrode is a typical "mixed potential."

MINNEAPOLIS, MINN. RECEIVED NOVEMBER 7, 1940

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

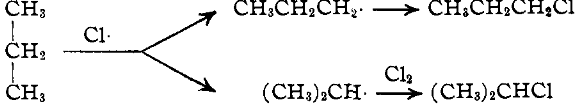
Reactions of Atoms and Free Radicals in Solution. II. The Non-Isomerization of Free Alkyl Radicals in Solution

BY M. S. KHARASCH, STEPHEN S. KANE[1] AND HERBERT C. BROWN

In the first paper of this series,[2] the photochemical chlorination and the peroxide-catalyzed chlorination of primary active amyl chloride were studied. The fact that the substitution of a chlorine atom for a hydrogen atom on the asymmetric carbon atom results in an inactive product was interpreted as support for the hypothesis that the reaction proceeds through a chain mechanism involving the momentary existence of a free alkyl radical.

$$Cl_2 \xrightarrow{h\nu} 2Cl\cdot$$
$$R_1R_2R_3C^*H + Cl\cdot \longrightarrow R_1R_2R_3C\cdot + HCl$$
$$R_1R_2R_3C\cdot + Cl_2 \longrightarrow R_1R_2R_3CCl + Cl\cdot$$

In drawing this conclusion from the experimental results, the tacit assumption was made that the substituent enters the molecule in the position left vacant by the removal of the hydrogen atom; in other words, that no rearrangement of the free radical occurs in the process of formation of the product. On the basis of this assumption the proportions of *n*-propyl and isopropyl chlorides in the chlorination product of propane should be the same as the proportions of the corresponding free radicals first formed.



Recently, however, Glazebrook and Pearson[3] have reported that free radicals may undergo an isomerization with the result that the structure of the final product is not necessarily determined by

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[1] This paper is part of a dissertation submitted by Stephen S. Kane to the Faculty of the Division of the Physical Sciences of the University of Chicago, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Brown, Kharasch and Chao, THIS JOURNAL, **62**, 3435 (1940).

[3] Glazebrook and Pearson, *J. Chem. Soc.*, 1777 (1936).

the structure of the free radical first formed. Thus, they report that isopropyl free radicals, prepared by the photolysis of diisopropyl ketone, isomerize when they react with mercury and yield di-*n*-propyl mercury. Furthermore, the observations that *n*-propyl bromide is partially isomerized at 262° into isopropyl bromide[4] and that isobutyl bromide is isomerized to *t*-butyl bromide under the influence of ultraviolet light[5] have been interpreted by them as phenomena with a similar cause. They suggest that the form in which the radical ultimately appears in a compound is governed by the nature of the element with which it has combined.

To quote: "It is the experience of organic chemists that the carbon atom C· in a *normal* group, $CH_3CH_2CH_2\cdot$, is less negative than that in the corresponding *iso*-group, $(CH_3)_2CH\cdot$ . . . *Hence, it is reasonable that the tautomerism which occurs on combination with an electropositive element (metal) involves the migration of hydrogen to yield the n-propyl derivative, whilst with an electronegative element (halogen) the iso-derivative is obtained*" (italics ours).

Without discussing the validity of the evidence upon which Glazebrook and Pearson base their argument, it may be stated that the general conclusion quoted is not supported by our studies of free radicals and their reactions. In order to obtain clear-cut evidence on the point at issue we have investigated the decomposition of *n*-butyryl peroxide and isobutyryl peroxide in carbon tetrachloride.

The thermal decomposition of acyl peroxides is now generally recognized to proceed through the formation of free radicals.[6] In carbon tetrachloride, the following reaction occurs[7]

$$[RCOO]_2 \xrightarrow{\Delta} 2R\cdot + 2CO_2$$
$$R\cdot + CCl_4 \longrightarrow RCl + Cl_3C\cdot$$
$$2Cl_3C\cdot \longrightarrow C_2Cl_6$$

By the decomposition of *n*-butyryl peroxide in carbon tetrachloride, only *n-propyl chloride* was formed; no trace of *isopropyl chloride* could be found. Similarly, the decomposition of isobutyryl peroxide in the same solvent yielded pure isopropyl chloride with no trace of the normal isomer.

These results may be accepted as evidence that no isomerization of free alkyl radicals occurs in the normal course of reactions in solution involving these intermediates. The fact that numerous reactions of the "atom-free radical type" which have been carried out both in the gas and liquid phases (such as the photochemical chlorination of aliphatic hydrocarbons) give practically identical yields of isomeric products suggests that this conclusion may safely be extended to reactions in the gas phase.

Examination of the higher boiling fractions obtained after the removal of the alkyl chloride and the excess carbon tetrachloride showed the presence of considerable quantities of ethyl *n*-butyrate and ethyl isobutyrate in the reaction products obtained from *n*-butyryl peroxide and isobutyryl peroxide, respectively. Investigation has revealed that the formation of these substances is due to a reaction of the peroxides with the ethyl ether used in their preparation. This observation is of considerable interest. Not only does it offer evidence that the decomposition of peroxides proceeds at least partly through the formation of free alkoxyl radicals ($RCOO\cdot$), but it suggests a means of detecting these free radicals. We are studying this reaction further and hope to report our results shortly.

Experimental Part

Preparation of Peroxides.—Both *n*-butyryl peroxide and isobutyryl peroxide were prepared by the action of the corresponding acid chlorides, dissolved in ether, on sodium peroxide. The preparation of 100 g. of acyl peroxide was carried out in five batches. Forty grams of the acid chloride and 200 cc. of absolute ether were placed in a 500-cc. flask which was fitted with a stirrer and surrounded by an ice–salt mixture. After the temperature had fallen to 0°, 20 g. of sodium peroxide was added, care being taken to keep the temperature low. When the reaction appeared to be complete, the excess of acid chloride was carefully decomposed by the slow addition of ice. The ether layer was separated, dried with calcium chloride, and the ether removed with a stream of dry air. The average yield of peroxide isolated was 65%.

Decomposition of *n*-Butyryl Peroxide.—During the course of seven hours, a mixture of 120 g. of *n*-butyryl peroxide and 120 cc. of carbon tetrachloride was added to 400 cc. of carbon tetrachloride boiling under a reflux condenser. The mixture was boiled for ten hours more, at which time the test for peroxide was negative. The product was fractionated through a column, 50 in. × 0.75 in., packed with a nickel gauze spiral.[8] Below the boiling point of carbon tetrachloride, but one constant boiling fraction (10.7 g., b. p. 46–46.5°) was isolated. This material was identified as *n*-propyl chloride by its refractive index (found $n^{20}D$ 1.3886; reported $n^{20}D$ 1.3889) and the

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[4] Eltekoff, *Ber.*, **6**, 1258 (1873); **8**, 1244 (1875); Michael and Leupold, *Ann.*, **379**, 263 (1911).

[5] Lucas and Salmon-Legagneur, *Compt. rend.*, **186**, 39 (1928).

[6] Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

[7] Böeseken and Gelissen, *Rec. trav. chim.*, **43**, 869 (1924).

[8] The column was constructed according to specifications furnished by Professor R. H. Ewell, Purdue University.

preparation of the alkyl mercuric chloride derivative[9] (found m. p. 140–3°; reported[10a,b,c] m. p. 140°, 143°, 147°).

After removal of the excess carbon tetrachloride, there was obtained a fraction of 15 g. distilling constantly at 119–120° which was identified as ethyl *n*-butyrate by hydrolysis and identification of *n*-butyric acid as the *p*-toluidide and ethyl alcohol as the 3,5-dinitrobenzoate.

The black residue remaining in the distillation flask after removal of the volatile products was extracted with ethyl alcohol. Twenty-five grams of hexachloroethane, m. p. 184°, was obtained.

Decomposition of Isobutyryl Peroxide.—The decomposition of isobutyryl peroxide in carbon tetrachloride was carried out in the same manner. A yield of 24 g. of isopropyl chloride, b. p. 35–36°, was obtained. Its identity was established by the preparation of the alkylmercuric chloride, m. p. 92–94°; a mixture with an authentic sample of isopropylmercuric chloride melted at 93–94°.

After removal of the more volatile fractions containing the alkyl chloride and carbon tetrachloride, there was obtained 14 g. of ethyl isobutyrate, b. p. 109°. The identification of the ester was confirmed by the isolation of ethyl alcohol and isobutyric acid upon hydrolysis. Extraction of the residue yielded 21 g. of hexachloroethane.

Summary

n-Butyryl peroxide reacts with carbon tetrachloride to form as primary products *n*-propyl chloride and hexachloroethane. Similarly isobutyryl peroxide forms isopropyl chloride and hexachloroethane. The formation of the *pure* alkyl chloride in each case is advanced as evidence that isomerization of free radicals does not occur in the course of reactions involving these intermediates.

The isolation of ethyl *n*-butyrate and ethyl isobutyrate from the action of ethyl ether on the corresponding peroxides is interpreted as indicating that the decomposition of the alkyl peroxides proceeds at least partially through the production of free alkoxy radicals.

CHICAGO, ILLINOIS RECEIVED NOVEMBER 19, 1940

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[9] Shriner and Fuson, "Identification of Organic Compounds," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 158.

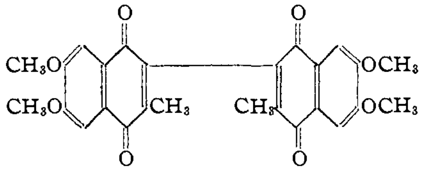
[10] (a) Marvel, Gauerke and Hill, THIS JOURNAL, **47**, 3009 (1925); (b) Goret, *Bull. sci. pharmacol.*, **29**, 297 (1922); (c) Slotta and Jacobi, *J. prakt. Chem.*, **120**, 249 (1929).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XXIV. Attempts to Prepare Desapogossypolone Tetramethyl Ether[1]

BY ROGER ADAMS, T. A. GEISSMAN, B. R. BAKER AND H. M. TEETER

In the previous paper the desirability of synthesizing desapogossypolone tetramethyl ether (I) in order to establish directly the presence of a binaphthyl nucleus in gossypol was explained and an unsuccessful approach to the problem was described. A second method of synthesis now has been devised and studied but failure of the next to the last step prevented its completion. The projected series of reactions are shown by formulas II–XV.



I

Veratrol (II) was converted to propioveratrone (III) by means of propionyl chloride in the presence of aluminum chloride. This, in turn, was brominated in chloroform to the α-bromopropioveratrone (IV) which was condensed with sodio-malonic ester in benzene to compound V. This substance (V) was not isolated but was saponified in a crude state and the corresponding malonic acid heated to cause decarboxylation to β - methyl - β - (3,4 - dimethoxybenzoyl) - propionic acid (VI). Clemmensen reduction of this last product gave β-methyl-γ-(3,4-dimethoxyphenyl)-butyric acid which was esterified without purification to the methyl ester (VII). Condensation of the methyl β-methyl-γ-(3,4-dimethoxyphenyl)-butyrate with ethyl formate in presence of sodium ethoxide gave methyl α-formyl-β-methyl-γ-(3,4-dimethoxyphenyl)-butyrate (VIII). Cyclization of compound VIII proceeded readily with a mixture of phosphoric and sulfuric acids to give the ester of 1,2-dihydro-2-methyl-6,7-dimethoxy-3-naphthoic acid (IX). In actual practice sometimes ethyl formate, sometimes amyl formate was used in preparing the formyl derivative. As a consequence, some *trans*-esterification

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[1] For previous paper in this series see Adams and Geissman, THIS JOURNAL, **61**, 2083 (1939).