react readily with proteins in neutral aqueous solution at room temperature. Esterification of the carboxyl groups appeared to be the predominating reaction. Since little attention had previously been given to the use of epoxides as esterifying agents,[2,3] model experiments were performed in which fatty acids and amino acids were treated with ethylene oxide, 1,2-propylene oxide, or epichlorohydrin in aqueous solution or suspension at room temperature.

In agreement with Brönsted,[2] dissociation of the acids was found to favor the reaction. Thus in four days acetic acid alone (0.06 *M*) was only 3% esterified by a 30-fold excess of propylene oxide, while, in the presence of a small amount of alkali metal ions, esterification of the acid approached completion. This catalytic action was produced not only by hydroxides directly but also by neutral salts, most readily by halides, which yield hydroxyl ions with the excess reagent according to the equation

$$CH_3—\underset{\diagdown O \diagup}{CH}—CHR + X^- + H_2O \longrightarrow CH_3CHOH—CHRX + OH^-$$

Possibly because simple synthetic methods have not been available, many monoesters of lower fatty acids with 1,2-diglycols are not known. As examples of the possible preparative use of the reaction of epoxides with fatty acids, ethylene glycol monovalerate and propylene glycol-1-monobutyrate were synthesized as follows:

The fatty acid (0.1) mole was treated in water solution or suspension with 0.01 mole NaOH and 1 to 2 moles of the epoxide. After standing four to six days at room temperature (with occasional shaking if the system was biphasic), the solution had become neutral through esterification of the free acid. The ester was then extracted with ether, washed with potassium carbonate, dried and distilled.

Both esters boiled at 56 to 57° (0.5 to 1 mm.). They were isolated in 58 to 63% yield. The refractive index at 25° was 1.4300 for ethylene glycol monovalerate and 1.4246 for propylene glycol-1-monobutyrate. *Anal.* Calcd. for $C_7H_{14}O_3$: C, 57.5; H, 9.6; saponification number, 384. Found for ethylene glycol monovalerate: C, 57.2; H, 9.6; saponification number, 387. Found for propylene glycol 1-monobutyrate: C, 57.0; H, 9.7; saponification number, 386.

In order to demonstrate that the addition of acids to unsymmetrical epoxides, *e. g.*, propylene oxide, occurred on carbon atom 1 in aqueous solution as it is known to do in anhydrous media, propylene glycol 1-monobutyrate was also prepared by refluxing an alcoholic solution of 1-chloro-2-propanol and sodium butyrate. The product, obtained in poor yield, boiled at 57° (1 mm.) and showed a refractive index of 1.4245.

Titrations and *p*H measurements demonstrated that amino acids or acylated amino acids were also readily esterified by epoxides. Thus, the interaction of propylene oxide with benzoyl-*d,l*-alanine, in the presence of one-tenth of the equivalent amount of sodium hydroxide, led to the disappearance of the undissolved material within one day. After three days the *p*H of the mixture had risen from 3.5 to 7.

In contrast to the carboxyl groups, the amino groups, determined by the Van Slyke manometric method,[4] appeared to react much more readily in the uncharged state, *i. e.*, in alkaline solution or only after all acids originally present had been "neutralized" by combination with the epoxide. Complete disappearance of the primary amino groups of 0.08 *M* solutions of monosodium glutamate or of alanine in the presence of sodium acetate (0.08 *M*) occurred within two days of treatment with excess propylene oxide (3 *M*). Surprisingly, the dipolar ion did not react as readily in the absence as in the presence of other electrolytes.

Attempts to isolate the epoxide derivatives of amino acids in pure form were unsuccessful since neither they nor a number of their derivatives could be made to crystallize. The products were very soluble in water and alcohol and could not be distilled without decomposition or molecular rearrangement.

WESTERN REGIONAL RESEARCH LABORATORY
BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY
AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
ALBANY 6, CALIFORNIA RECEIVED MAY 12, 1944

(2) Brönsted, Kilpatrick and Kilpatrick, THIS JOURNAL, **51**, 428 (1929).

(3) Bauer and Mauthe, U. S. Patent 1,979,601 (1934).

(4) Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

A Method of Synthesis for Aromatic Aminoaldehydes and Aminoketones

BY WU HAO-TSING

It has been found that the reaction of hydrogen cyanide or nitriles, hydrogen chloride and phenols,[1] which has always been considered to be specific for aromatic hydroxy compounds, can be extended to the aromatic amine, aniline. Preliminary studies have demonstrated that *p*-aminobenzaldehyde and *p*-aminoacetophenone can be prepared by this method, and it seems likely that the reaction can be extended. Further work on the improvement of the yield and on the synthesis of related compounds is now in progress.

It is believed that an addition compound (I) is first produced and this on heating rearranges to the carbon substitution product (II) which on hydrolysis gives the carbonyl derivative (III).

$$RCN^a + C_6H_5NH_2 \xrightarrow[\text{Dry ether}]{HCl} \underset{\text{I}}{R—C(=NH)—N(H)—C_6H_5} \xrightarrow{\text{heat}} \underset{\text{II}}{R—C(=NH)—C_6H_4NH_2} \xrightarrow{H_2O} \underset{\text{III}}{R—C(=O)—C_6H_4NH_2}$$

[a] In the two experiments reported R has been hydrogen and a methyl group. It is thought other alkyl groups or possibly aryl groups can be used.

Experimental

(1) **Preparation of *p*-Aminobenzaldehyde.**—Ten grams of dry hydrogen cyanide and 9.3 g. of aniline were added to 70 cc. of ether which had been previously saturated with dry hydrogen chloride. When the mixture thus obtained was enclosed in a bottle and gently heated for several hours, an oily liquid, brown in color, was precipitated. This oily liquid was then transferred into a sealed tube, and heated at 250–300° for one hour. The contents of the sealed tube were afterward put into a solution of potassium hydroxide, boiled for a few minutes, extracted with ether and recrystallized from water in the form of leaflets. These melted at 70–72° (percentage of nitrogen determined, 11.60; calculated, 11.57).

(2) **Preparation of *p*-Aminoacetophenone.**—*p*-Aminoacetophenone was prepared by the reaction of aniline

(1) Hoesch, *Ber.*, **48**, 1122 (1915).

upon acetonitrile in the same manner as the experiment just described. It melted at 106–107° (percentage of nitrogen determined, 10.39; calculated, 10.37).

It is absolutely essential that all materials used in these experiments be anhydrous and that care be taken to prevent the introduction of moisture in transferring the addition compounds to the sealed tubes, in order to have success with this reaction.

NATIONAL UNIVERSITY OF CHEKING
CHINA

RECEIVED JANUARY 3, 1944

COMMUNICATIONS TO THE EDITOR

RESYNTHESIS OF DESTHIOBIOTIN FROM DIAMINOPELARGONIC ACID[1]

Sir:

Work in this Laboratory has demonstrated[2] that desthiobiotin, derived from biotin by hydrogenolysis of the sulfide linkage,[3] is equally as effective as biotin in promoting the growth of yeast. Desthiobiotin has been shown to be 4-methyl-5-imidazolidone-2-caproic acid, and is converted by acid or alkaline hydrolysis to ζ,η-diaminopelargonic acid.[3]

In view of the high yeast-growth-promoting activity of desthiobiotin, it became of interest particularly from the standpoint of possible synthetic approaches to desthiobiotin, to investigate the effect of phosgene on the diaminopelargonic acid derived from desthiobiotin, since it has been shown[4] that nearly quantitative yields of biotin can be obtained by treatment with phosgene of the sulfur-containing diamino acid derived from biotin.

Diaminopelargonic acid was prepared in good yield from pure desthiobiotin[2] by hydrolysis with barium hydroxide.[3] The product was isolated as the sulfate, which crystallized in small diamond-shaped plates, micro m. p. 245–246°.

For the treatment with phosgene, 15 mg. of the diaminopelargonic acid sulfate was dissolved in 2 cc. of aqueous 10% sodium carbonate and phosgene gas was passed into the solution until the solution became acid to congo red. The clear solution was concentrated *in vacuo* to a volume of approximately 0.5 cc. Crystalline material separated from the solution and was removed and washed with a few drops of water. The combined washings and mother liquors were extracted continuously with ether for two hours; a small amount of crystalline material separated in the ether extract. The crystalline fractions were combined, dissolved in methanol and filtered, and the filtrate was concentrated to dryness. The residue was crystallized from a few drops of hot water, washed with water, and dried. The yield of product in the form of long, colorless needles, micro m. p. 156–158°, was 7.4 mg. (66% of the theoretical yield).

The reaction product possessed the same crystalline form, solubility, and melting point as desthiobiotin. A mixture of the reaction product with a sample of pure desthiobiotin, micro m. p. 156–158°, showed no depression of the melting point. Furthermore, the resynthesized material possessed the same yeast-growth-promoting activity as desthiobiotin. The diaminopelargonic acid from which it was synthesized, on the other hand, exhibited approximately 10% of the activity of desthiobiotin under the same conditions of assay and at levels which produced half-maximum growth.

It is concluded from these data that the chief product formed by the action of phosgene on the diaminopelargonic acid is desthiobiotin. The yield obtained suggests the use of this reaction as a step in the total synthesis of desthiobiotin.

DEPARTMENT OF BIOCHEMISTRY
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK 21, N. Y. DONALD B. MELVILLE

RECEIVED JULY 17, 1944

(1) The desthiobiotin used in this investigation was prepared from natural biotin generously supplied by Merck and Company, Inc. Appreciation is also expressed to Dr. Karl Dittmer and Mrs. Glenn Ellis for carrying out the microbiological assays.

(2) Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

(3) Du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *J. Biol. Chem.*, **146**, 475 (1942).

(4) Melville, Hofmann and du Vigneaud, *Science*, **94**, 308 (1941).

THE MECHANISM OF THE ALKYLATION OF PARAFFINS WITH OLEFINS IN THE PRESENCE OF ALUMINUM CHLORIDE

Sir:

The previously proposed mechanisms[1] for the catalytic alkylation of paraffins are unsatisfactory either in explaining how the reaction occurs or accounting for the structure of the products obtained. An investigation of the reaction of alkyl chlorides with olefins and of isoparaffins with chloroölefins has now led to the conclusion that the alkylation of isoparaffins with olefins in the presence of aluminum chloride proceeds via the conversion of the paraffin to an alkyl chloride. The mechanism is outlined below for the reaction of isobutane with ethylene. Similar reactions occur with other paraffins and olefins.

The *t*-butyl chloride formed in Eq. 3 starts a new cycle by reacting with ethylene as in Eq. 2. Ethane is produced only in the initiating step and the amount formed will therefore be small.

(1) (a) Ipatieff and Grosse, THIS JOURNAL, **57**, 1616 (1935); (b) Birch and Dunstan, *Trans. Faraday Soc.*, **35**, 1013 (1939); (c) Caesar and Francis, *Ind. Eng. Chem.*, **33**, 1426 (1941); (d) Mc Allister, Anderson, Ballard and Ross, *J. Org. Chem.*, **6**, 647 (1941).