of hydrated barium hydroxide was added. The barium sulfate was removed and 250 g. of sodium carbonate added. Upon evaporation to dryness, 375 g. of crude sodium salt was obtained.

m-**Hydroxybenzoic Acid.**—One hundred twenty-nine and six-tenths grams (0.4 mole if pure) of the above salt was fused with a mixture of 200 g. of sodium hydroxide and 168 g. of potassium hydroxide at 310° for two hours. After cooling the solid was dissolved in 800 cc. of water and 700 cc. of concentrated hydrochloric acid added. On cooling the aqueous solution was extracted with three 200-cc. portions of ether. The ether on evaporation gave 20 g. (36%) of crude acid m. p. 172–182°; recrystallized twice from benzene–ether, m. p. 202° uncor.

When treated with methyl sulfate and alkali *m*-methoxybenzoic acid was obtained, m. p. 101–102°; neutral equivalent calcd., 152.0; found, 150.0.

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

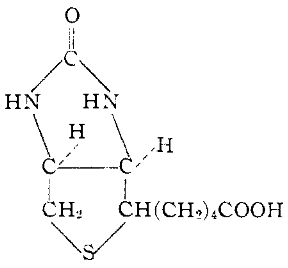
RECEIVED JUNE 8, 1944

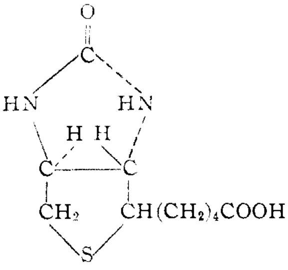
COMMUNICATIONS TO THE EDITOR

BIOTIN. III. *cis* and *trans* FORMS RELATED TO *dl*-BIOTIN

Sir:

It was stated in a previous publication[1] that it was believed that compounds having two five-membered saturated heterocyclic nuclei fused through adjacent carbon atoms, as in biotin, would exist only in *cis* forms of the rings, as in structure I.

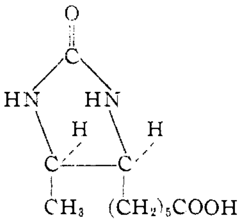

I

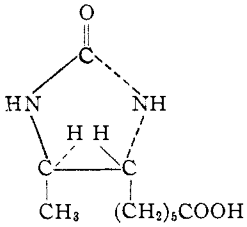

II

Originally two racemates related to biotin, namely, *dl*-biotin, m. p. 232° (*Anal.* Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.46. Found: C, 49.33; H, 6.39; N, 11.68), and *dl*-allobiotin, m. p. 194–196° (*Anal.* Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.46. Found: C, 49.36; H, 6.50; N, 11.39), were obtained, one of which yielded biotin on resolution. The series of reactions[2] which led to the formation of these racemates is described in another communication. A third racemate, *dl-epi*allobiotin (decomposes without melting starting at 195°) (*Anal.* Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.46. Found: C, 49.23; H, 6.75; N, 11.21), having the structure of biotin has been derived from the reduction product of the dehydro isomer[2] melting at 162–163°. The other reduction product from this isomer yielded *dl*-allobiotin.

Thus, three racemates corresponding to six of the eight theoretically possible isomers are known. It is evident that one or two of the known racemic pairs must have a *trans* configuration of its nitrogen atoms as represented by structure II.

This new racemate has been correlated to *dl*-allobiotin[2] by hydrogenolysis[3] with Raney nickel catalyst. Both the new racemate and *dl*-allobiotin gave the same desthio derivative, III or IV, which is called *dl*-desthioallobiotin; m. p. 165–166° (*Anal.* Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05: H, 8.47; N, 13.08. Found: C, 55.86; H, 8.25; N, 12.76.


III


IV

dl-Biotin gave *dl*-desthiobiotin which also melted at 165–166° (*Anal.* Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.04; H, 8.52; N, 13.22). However, these two compounds showed a mixed melting point depression of twenty degrees. Dr. Jacob L. Stokes of this Laboratory found that *dl*-desthioallobiotin was inactive for the growth of yeast, while *dl*-desthiobiotin was one-half as active as *d*-desthiobiotin.[4]

From these results it is evident that the new racemate is epimeric at carbon atom 2 of *dl*-allobiotin; therefore, it will be called *dl-epi*allobiotin.

The fact that *d*-desthiobiotin methyl ester[3] and *d*-desthiobiotin ($[\alpha]^{31}_{D}$ +10.4 (*c*, 1.7525 in 0.1 *N* sodium hydroxide)) have a low but definite optical activity is evidence that inversion of the nitrogen atoms did not take place during the hydrogenolysis. Furthermore, the latter compound does not agree in melting point[4] or mixed melting point with either of the *dl* derivatives.

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[1] Paper I, Harris, Wolf, Mozingo and Folkers, *Science*, **97**, 447 (1943).

[2] Harris, *et al.*, Paper II, THIS JOURNAL, **66**, 1756 (1944).

[3] du Vigneaud, *et al.*, *J. Biol. Chem.*, **146**, 475 (1942); Mozingo, *et al.*, THIS JOURNAL, **65**, 1013 (1943).

[4] Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

A detailed description and correlation of the stereoisomers obtained in the synthesis of biotin will appear later.

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DONALD E. WOLF
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MERCK & CO., INC. GLEN E. ARTH
RAHWAY, NEW JERSEY KARL FOLKERS

RECEIVED AUGUST 29, 1944

STUDIES ON THE POLYBROMINATION OF ALKYLBENZENES. PRELIMINARY REPORT

Sir:

In connection with studies on the alkylation of benzene (and other aromatic nuclei), we have for some time been interested in developing new and more generally useful derivatives of alkyl and polyalkylbenzenes. The polybromination of such compounds has now been explored in a preliminary manner and the rather surprising observation made that all *secondary* and *tertiary* alkyl groups are replaced by bromine while *primary* groups are retained. In all cases the free positions of the ring are filled at the same time. For example, when 1 g. of isopropylbenzene is added to 7 ml. of bromine and 0.2 g. of iron powder at 0°, a good yield of hexabromobenzene, m. p. 317°, is obtained; with *n*-propylbenzene the *n*-propyl group is apparently unaffected and the product appears to be pentabromo-*n*-propylbenzene, m. p. 95°. *s*-Butyl- and *t*-butylbenzene also afford hexabromobenzene, while the *n*-butyl and *i*-butyl compounds give derivatives melting at 78 and 76°, respectively, mixed m. p. 49–52°. Over thirty-five alkyl and polyalkylbenzenes having C_1 to C_5 alkyl substituents in various combinations have been studied without encountering a single exception to the rule cited above. As a matter of further interest, the procedure has been applied to a number of synthetic mixtures of isomeric alkylbenzenes. Each component was found to behave normally, making it possible, for example, to detect readily 10% or less of *n*-propylbenzene in isopropylbenzene. Obviously this technique should have considerable diagnostic value in studying the fate of alkyl groups in alkylation reactions and in the rearrangements of alkylbenzenes.

The various reaction products which have been accumulated are soon to be examined more fully as well as a number of the obvious applications of the general method, *e. g.*, the study of products obtained in the aluminum chloride rearrangement of dipropylbenzenes. Although this work has been interrupted temporarily, we hope to report on these investigations in detail at a later date.

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NOTRE DAME, INDIANA JAMES G. ANDERSON

RECEIVED SEPTEMBER 5, 1944

POLAROGRAPHIC REDUCTION OF CARBON DIOXIDE

Sir:

We have been engaged for some time in the study of the reduction of carbon dioxide at the dropping mercury cathode. On the basis of a large number of polarograms obtained by means of a Heyrovsky Polarograph of the Sargent Co. with solutions of carbon dioxide in 0.1 molar tetramethylammonium chloride, we have arrived at the following definite conclusions: carbon dioxide exhibits well-defined reduction waves with a half-wave potential of remarkable constancy: -2.24 ± 0.01 volt referred to the saturated calomel electrode. This is the average of ten independent determinations with varying amounts of carbon dioxide. When hydrogen is passed through the substituted ammonium salt solution before the dissolution of carbon dioxide, the waves are equally well defined, but the half-wave potential is somewhat less negative: -2.18 ± 0.02 volt referred to the saturated calomel electrode. This is the average of seven independent determinations, with varying amounts of hydrogen and carbon dioxide.

The slope dE/du, or $i_d\, dE/di$, at the half-wave (E = cathodic potential, u = ratio of the current i to the diffusion current i_d, $u = 0.5$ at the half-wave) varies, according to the amount of carbon dioxide, between rather wide limits: the lowest recorded slope is 0.359 v. and the highest is 0.614 v. For an ordinary reduction involving one molecule, two electrons and two hydrogen ions, in a medium of constant *p*H, this slope should be $2RT/F$ or 0.051 v. (R = gas constant, T = absolute temperature, F = 1 faraday).[1]

The discussion of the various features of these polarographic waves, their detailed mathematical analysis, and our conclusions concerning the mechanism of carbon dioxide reduction at the dropping mercury cathode will be presented in subsequent communications.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF OREGON PIERRE VAN RYSSELBERGHE
EUGENE, OREGON GEORGE J. ALKIRE

RECEIVED AUGUST 28, 1944

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(1) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, pp. 146, 194, etc.