ethylidene bond of isoquinine takes place more slowly than similar addition to the vinyl group of quinine.

Although the reduction of isoquinine has been studied,[1] the use of an unsymmetrical molecule as an addendum has not been described. From the material available we were not able to identify epimeric C-3 derivatives as Henry and co-workers[1] did with dihydroquinine. Subsequent removal of halogen from iodohydroquinine (prepared from isoquinine) regenerated isoquinine and gave some niquine.

The separation of the α and α' isomers[2] of 10-iodohydroquinine by recrystallization from benzene had been carried out in this Laboratory prior to the publication of Reyman and Suszko[3]; the specific rotations observed ($-218°$ and $-19°$) were practically identical with the values reported by the Polish investigators. $[\alpha]$ $-$ 19° is the value for α'-iodohydroquinine, having one mole of benzene of crystallization. When benzene was removed by evaporating an ether solution to dryness, the product melted at 130° and $[\alpha]_D$ was $-22.3°$. The $-218°$ fraction was most advantageously crystallized from acetone or alcohol for final purification.

The strongly levorotatory α-isomer loses hydrogen iodide to give predominantly niquine, and the α'-isomer gives predominantly isoquinine.[3,4] In our experience it was not possible to get the exclusive transformation Suszko reported. During storage for a number of months, the more levo of the isomeric iodohydroquinines appears to be the less stable, and this fact has been noted previously for the quinidine series in the case of bromodihydroquinidine.[5]

Iodohydroquinine from Isoquinine.—Ten-gram portions of isoquinine, heated on a water-bath for two hours with 60 g. of hydriodic acid[6] (d. 1.7), gave only a 35% yield of the yellow crystalline iodohydroquinine dihydriodide. Continued heating for thirty minutes increased the yield to 50%. Unchanged isoquinine, recovered from the final liquor, accounted for 25–30% of the original isoquinine. This slow reaction rate is in contrast to the 70% yield obtained in two hours when quinine was the starting material. The specific rotation of the iodohydroquinine base in alcohol was $-150°$.

Anal. Calcd. for $C_{20}H_{25}N_2O_2I \cdot C_6H_6$: I, 24.0. Found: I, 24.4.

On treating this sample of iodohydroquinine with alcoholic potassium hydroxide, isoquinine and a small amount of niquine were obtained.

CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY
MELLON INSTITUTE OF INDUSTRIAL RESEARCH
PITTSBURGH, PENNA. RECEIVED JUNE 29, 1943

(1) Henry, Solomon and Gibbs, *J. Chem. Soc.*, 592 (1937).

(2) In the absence of a uniform scheme of nomenclature, we have followed the method of Goodson, who arbitrarily used the prefix α for the isomer of higher rotation and α' for the other isomer: Goodson, *ibid.*, 1094 (1935).

(3) Reyman and Suszko, *Bull. Intern. Acad. Polonaise*, **A**, 360 (1935).

(4) Podlewski and Suszko, *Rec. trav. chim.*, **55**, 392 (1936).

(5) Gibbs and Henry, *J. Chem. Soc.*, 240 (1939).

(6) Skraup, *Monatsh.*, **14**, 428 (1893); Rosenmund and Kittler, *Arch. Pharm.*, **262**, 18 (1924).

The Role of Glycine in Protein Structure

BY HANS NEURATH

Recent discussions of protein structure have emphasized the importance of the amino acid side chains in determining the structure of fibrous and globular proteins.[1-4] The position of the side chains along a polypeptide chain is determinant for the types of lateral bonds and the extent of internal rotation of polypeptide chains. A skeletal polypeptide chain, stripped of side chains, is endowed with a considerable degree of internal rotation about single valence bonds of the constituent carbon and nitrogen atoms. However, in a genuine polypeptide chain, equipped with the full complement of side chains, internal rotation is greatly restricted due to the space requirements of the amino acid residues. Various configurations, previously proposed for folded polypeptide chains and chain net-works, had, accordingly, to be excluded, since they resulted in an excessive crowding of component atoms and groups.[1,5] Such steric limitations apply equally to fully extended polypeptide chains, if they be made up of a combination of alternating *d*- and *l*-amino acids, but not to polypeptides comprised of less than four amino acid residues. In the latter, terminal side chains are free to branch out and, by virtue of rotation about the α,β carbon bond, to orient themselves as demanded by their space requirements.

The space requirements of amino acids depend on their average chain length and their cross-sectional area beyond the α-carbon atom.[1] The amino acid with the smallest cross-sectional area is glycine, since at the place where other amino acids carry a side chain, glycine has merely a hydrogen atom of about 4 sq. Å. cross-sectional

(1) Neurath, *J. Phys. Chem.*, **44**, 296 (1940).

(2) Bull, "Advances in Enzymology," Vol. I, Interscience Publishers, New York, N. Y., p. 1 *et seq.*

(3) Astbury and Bell, *Nature*, **147**, 696 (1941).

(4) Chibnall, *Proc. Roy. Soc.* (London), **B131**, 136 (1942).

(5) Mack, *Ohio J. Sci.*, **41**, 183 (1941); Huggins, *Ann. Rev. Biochem.*, **11**, 32 (1942).

area (as compared to about 11.5 sq. Å. for the methyl group of alanine, and about 35 sq. Å. for the benzene nucleus of phenylalanine). It occurred to us that the presence of glycine residues may confer upon a polypeptide chain a considerable degree of flexibility and internal rotation, since, wherever a glycine residue occurs, a hydrogen atom is taking the place of a more complex residue R. Hence, free rotation about —C(HR)—N(H)— bonds should be possible to nearly the same extent as if a polypeptide chain were devoid of a side chain. Accordingly, the presence of glycine residues, and their distribution along the chain, may be factors influential in determining the specific pattern of folding of polypeptide chains.

It is of interest to examine certain experimental and theoretical aspects of this hypothesis in relation to the problem of protein structure:

1. The proper distribution of glycine residues would permit any combination of side chains which, otherwise, would have to be excluded because of steric hindrance. For instance, while it would be extremely difficult to depict a situation where any two aromatic or heterocyclic amino acids, separated by any third amino acid, X, could follow each other along a folded polypeptide chain without causing steric interference, such a combination could occur if X is glycine. In such an instance, free rotation would allow them to assume juxtapositions with respect to the plane of the main chain from which they protrude. It would also be conceivable that natural and unnatural amino acids might be incorporated together in a polypeptide chain if glycine residues are interdispersed to provide internal rotation.[6]

2. The concept of internal rotation due to glycine might account for the selective orientation of side chains in monomolecular protein films—polar side chains toward the water, non-polar side chains toward the air phase.[7]

It also obviates the necessity for concluding that certain proteins such as keratin and myosin consist of an even number of polar and non-polar side chains, arranged alternately along the main chains.[8]

3. It was noted that silk fibroin is devoid of a diffraction period longer than 2 × 3.5 Å. along the fiber axis although a repeating pattern at about 16 × 3.5 Å. would have to be expected if the residues in this protein, of which about 44% are glycine and 25% alanine, were distributed in a regular fashion.[8] This could be explained by ascribing to glycine a position, determined by a specific stereochemical function, in preference to the position required by a periodical arrangement of amino acid residues.

While glycine thus *facilitates* folding of polypeptide chains, more reactive amino acid residues probably determine the *mode* of folding, by mutual interaction.

The present hypothesis rests on the assumption that glycine is a natural constituent of all proteins. While certain proteins have been reported to be devoid of glycine,[9] it has to be recalled that most of these analyses were carried out with methods which would fail to reveal a glycine content of several per cent.[10,11] Therefore, this argument remains open pending further analytical data. It may be of significance, however, that the large space requirements of proline and hydroxyproline in the gelatin molecule (about 32%) are counterbalanced by a comparable content of glycine (about 25%). Similarly, elastin contains 29% of glycine as compared to 15% of proline and 2% of hydroxyproline.[12]

The present hypothesis does not necessarily conflict with the Bergmann–Niemann hypothesis[13] of the periodicity of occurrence of amino acids in polypeptide chains. Yet, a very high degree of selectivity in the synthesis of proteins would have to be evoked in order to place amino acids in the positions called for by a combined demand of periodicity and stereochemical space requirements.

The unique stereochemical conditions caused by the presence of glycine in a peptide chain have already been recognized by Bergmann in studying the antipodal specificity of proteolytic enzymes.[14] Optically active amino acids, when present in the *d*-form, inhibit through steric hindrance the action of enzymes that are adapted to substrates containing *l*-amino acids. How-

(6) Pauling (THIS JOURNAL, **62**, 2643 (1940)), cognizant of the large space requirements of proline and hydroxyproline, suggested that these amino acid residues occupy terminal chain positions in normal and immuno-serum globulins. As an alternative hypothesis one could assume that they occupy positions adjacent to glycine residues.

(7) Neurath and Bull, *Chem. Rev.*, **23**, 391 (1938).

(8) Astbury, "Advances in Enzymology," Vol. III, Interscience Publishers, New York, N. Y., p. 63 ff.

(9) *Cf.* Patton, *J. Biol. Chem.*, **108**, 267 (1935).

(10) Personal communication of Dr. Max Bergmann.

(11) Egg albumin, for instance, has been reported to be devoid of glycine whereas the solubility method of Bergmann and Stein revealed a glycine content of about 3.1% (Stein, *Proc. Fifth Ann. Meeting Am. Soc. Brewing Chem.*, May 25–27 (1942)), equal to 18–19 residues per protein molecule (45,000 molecular weight).

(12) Stein and Miller, *J. Biol. Chem.*, **126**, 599 (1938).

(13) Bergmann and Niemann, *ibid.*, **115**, 77 (1936).

(14) Bergmann, *Science*, **79**, 479 (1934); Bergmann and Fruton, *J. Biol. Chem.*, **117**, 189 (1937).

ever, glycine-containing substrates are split under these conditions since glycine contains no side chain in such a spatial arrangement that it could prevent an approach of the enzyme.

It is a pleasure to acknowledge many valuable suggestions which Dr. Max Bergmann has offered in a discussion of this problem.

DEPARTMENT OF BIOCHEMISTRY
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NEW COMPOUND

4-Phenylphenyl Butyrate

This compound was prepared in 81% yield by the interaction of 4-phenylphenol and butyryl chloride[1] in pyridine solution with 1,4-dioxane as diluent.[2] The crude product was dissolved in benzene, and the resulting solution was washed with dilute hydrochloric acid and sodium hydroxide solution and decolorized with Norite. After removal of the benzene on the steam-bath, the product was crystallized four times from 30–60° ligroin; colorless platelets resulted; m. p. 59–60.3°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.67. Found: C, 79.83; H, 6.85.

(1) Gilman and Blatt, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 2d ed., 1941, p. 147.
(2) Hazlet, Hensley and Jass, THIS JOURNAL, **64**, 2449 (1942).

DEPARTMENT OF CHEMISTRY
STATE COLLEGE OF WASHINGTON
PULLMAN, WASHINGTON
STEWART E. HAZLET
LEE C. HENSLEY

RECEIVED JULY 20, 1943

COMMUNICATION TO THE EDITOR

THERMAL PROPERTIES OF ISOPENTANE

Sir:

Anyone not completely familiar with the field, on reading the paper by Guthrie and Huffman on page 1143 of the June, 1943, issue of THIS JOURNAL might receive a wrong impression. We have carefully reviewed our work published on isopentane in THIS JOURNAL and find no reason to doubt the data there reported. The facts are that two independent groups of workers using different calorimeters have observed an anomaly in the thermal behavior of isopentane. A third group of workers using a different calorimeter have failed to observe this phenomenon. The second independent series of measurements was made in our laboratory but in a different calorimeter (Gold calorimeter C). The work was done by M. L. Sagenkahn and H. F. Zuhr. The third independent series of measurements is that of Guthrie and Huffman. After the present emergency we shall repeat again the work on isopentane using the Huffman type calorimeter.

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J. G. ASTON

RECEIVED AUGUST 6, 1943

NEW BOOKS

Organic Syntheses. Volume 23. LEE IRVIN SMITH, Editor-in-Chief, HOMER ADKINS, C. F. H. ALLEN, W. E. BACHMANN, NATHAN L. DRAKE, C. S. HAMILTON, R. L. SHRINER, H. R. SNYDER AND A. H. BLATT, Secretary to the Board. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1943. 124 pp. 15 × 23.5 cm. Price, $1.75.

In this last volume of this important series of Organic Syntheses are recorded specific directions for preparing thirty-nine different organic compounds These embrace representatives of the aliphatic, aromatic and heterocyclic series; and fifty-four contributors other than members of the publishing Board have taken part in the development and construction of the experimental technique described. The techniques proposed have been checked in each experiment by two independent workers. A short literature review accompanies each preparation and in many cases useful notes are inserted which serve to guide the experimenter in applying the experimental procedure recommended. All the procedures are clearly written, and the book should find a most useful service in every laboratory where organic synthesis is being applied and practiced.

TREAT B. JOHNSON