[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLUMBIA UNIVERSITY]

The Synthesis of *dl*-β-Cyclohexylalanine

BY DAVID SHEMIN AND ROBERT M. HERBST

While studying the preparation of *dl*-β-phenylalanine by the reduction of α-acetaminocinnamic acid[1] in the presence of Adams platinum oxide catalyst, the occasional formation of *dl*-β-cyclohexylalanine (hexahydrophenylalanine) was observed. Generally an unsaturated linkage in the side chain of an aromatic compound may be hydrogenated by catalytic methods without reduction of the aromatic nucleus. The rate of hydrogenation of the aromatic nucleus is so much slower than that of the unsaturated side chain that there is a sharp break in the rate of hydrogen uptake when the latter has been completely saturated.

When freshly prepared and still moist Adams catalyst was employed for the reduction of α-acetaminocinnamic acid, the rate of hydrogenation of even the phenyl group was so great that on numerous occasions no break in the rate of hydrogen uptake was apparent until the compound was completely hydrogenated. The reduction of the compound, both of the unsaturated side chain and of the phenyl group, was complete in about an hour and a half. After the same preparation of catalyst had been dried and allowed to stand in a desiccator for a week or longer, it showed the usual differential rate of hydrogenation of the side chain unsaturation and of the aromatic nucleus.

In view of the fact that *dl*-β-cyclohexylalanine has not been described, a brief characterization of the compound may be of value. Waser and Bräuchli[2] have described *l*-β-cyclohexylalanine (*l*-hexahydrophenylalanine), which they obtained by catalytic hydrogenation of *l*-tyrosine. A certain amount of confusion was introduced by their failure in an earlier paper[3] to realize that the hydroxyl group of the tyrosine was at least partially eliminated during the hydrogenation.

Experimental

N-Acetyl-*dl*-β-cyclohexylalanine.—A solution of 10 g. of α-acetaminocinnamic acid[1] (p. 1) in 75 cc. of glacial acetic acid containing about 0.25 g. of freshly prepared Adams platinum oxide catalyst was shaken with hydrogen under two to three atmospheres pressure in a Burgess–Parr hydrogenation apparatus. The theoretical amount of hydrogen (4 mols) was taken up in from one to two hours. After removal of the catalyst the solution was evaporated to dryness *in vacuo*. Recrystallization of the residue from hot water gave 9.5 g. of N-acetyl-*dl*-β-cyclohexylalanine as needles, m. p. 178°.[4,5]

Anal. Calcd. for $C_{11}H_{19}O_3N$: C, 62.0; H, 9.0; N, 6.6. Found: C, 62.0; H, 8.9; N, 6.6.

***dl*-β-Cyclohexylalanine.**—The amino acid was prepared by hydrolysis of the acetyl derivative with twenty parts of boiling normal hydrochloric acid for eight hours. The hydrochloric acid was removed as completely as possible by vacuum distillation. The remainder of the chloride was removed by treatment with silver oxide followed by hydrogen sulfide to remove silver ion. *dl*-β-Cyclohexylalanine was obtained by evaporation of the clear aqueous solution. On recrystallization from hot water it separated in the form of needles that tended to group together in bunches.

Anal. Calcd. for $C_9H_{19}O_2N$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.0; H, 9.8; N, 8.2.

The compound showed similarity to phenylalanine in its water solubility. It usually was necessary to employ relatively large volumes of boiling water to dissolve the compound completely, and evaporation of some of the solvent was necessary before crystallization took place.

N-Benzoyl-*dl*-β-cyclohexylalanine.—Benzoylation of *dl*-β-cyclohexylalanine was carried out in aqueous solution with benzoyl chloride in the presence of sodium bicarbonate. The benzoyl derivative crystallized from aqueous alcohol as plates, m. p. 182–183.5°.

Anal. Calcd. for $C_{16}H_{21}O_3N$: C, 69.8; H, 7.7; N, 5.1. Found: C, 69.6; H, 7.6; N, 5.1.

α - Phenylureido - β - cyclohexylpropionic Acid.—The phenyl isocyanate derivative of β-cyclohexylalanine was prepared by shaking an aqueous solution of the amino acid with a slight excess of phenyl isocyanate. The derivative crystallized from aqueous alcohol as prisms, m. p. 177.5° with decomposition.

Anal. Calcd. for $C_{16}H_{22}O_3N_2$: C, 66.2; H, 7.6; N, 9.6. Found: C, 66.1; H, 7.5; N, 9.5.

3-Phenyl-5-cyclohexylmethylhydantoin.—The phenylureido derivative was converted into the corresponding hydantoin by boiling in a mixture of equal parts of absolute alcohol and concentrated hydrochloric acid for several hours. After removal of the alcohol by distillation *in vacuo* the product separated from the reaction mixture in the form of needles or long prisms, m. p. 172.5° after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{16}H_{20}O_2N_2$: C, 70.6; H, 7.4; N, 10.3. Found: C, 70.7; H, 7.4; N, 10.2.

(1) Herbst and Shemin, *Org. Syntheses*, Vol. **19**, 67 (1939).
(2) Waser and Bräuchli, *Helv. Chim. Acta*, **7**, 740 (1924).
(3) Waser and Bräuchli, *ibid.*, **6**, 199 (1923).
(4) All melting points are corrected.
(5) Bernhard [*Z. physiol. Chem.*, **256**, 49 (1938)] reports the melting point of N-acetyl-*l*-β-cyclohexylalanine as 198–199°.

Summary

The preparation of *dl*-β-cyclohexylalanine and several derivatives is described.

NEW YORK, N. Y. RECEIVED JUNE 19, 1939

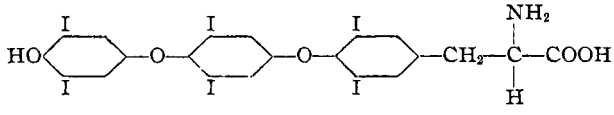
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLUMBIA UNIVERSITY]

An Analog of Thyroxine

BY M. BOVARNICK, K. BLOCH AND G. L. FOSTER

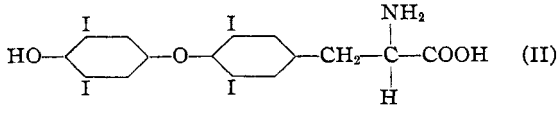
There have been numerous studies on the chemical constitution of thyroxine in relation to its physiological activity. A full discussion of this subject is given by Harington[1] in his monograph on thyroxine. He observes that the presence of certain chemical features in the molecule seems to be responsible for its specific physiological activity, namely, its iodine content, the special orientation of two of the iodine atoms in the ortho position to a phenolic group, the presence of the diphenyl ether linkage, and the α-amino acid residue.

It therefore seemed of some interest to see whether the following compound (I) might possess thyroxine activity.



(I)

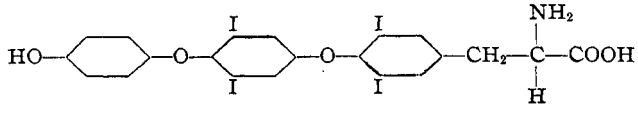
Comparing this with thyroxine (II) the chemical similarities are shown.



(II)

Physiologically, however, the three-ringed amino acid showed no significant activity.

One of the intermediate products in the synthesis is the following



(III)

Because of the parallel relationship between this and our final product (I) on the one hand, and 3,5-diiodothyronine and thyroxine on the other, it was thought worth while to test this physiologically. It showed no more activity than that displayed by the fully iodinated compound (I).

(1) Harington, "The Thyroid Gland," Oxford University Press, London, 1933, Chapter VII.

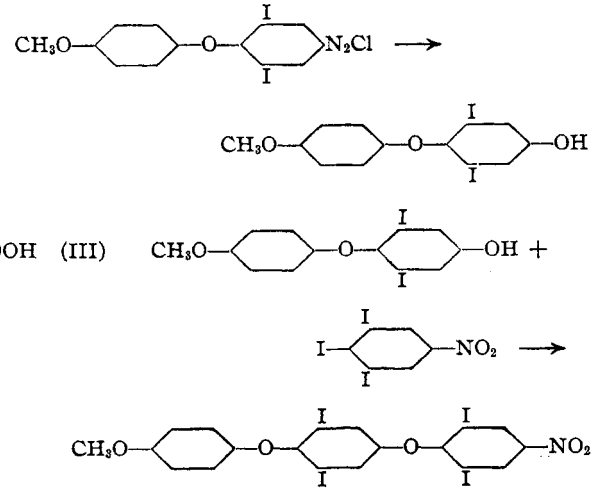
Experimental

Bio-assay.—Since the preliminary estimations, which were done by comparing the weight curves of test animals with thyroxine treated and normal controls, showed so little activity, the more complicated and tedious assay by basal metabolic rates was not undertaken.

Guinea pigs of about 300 g. weight were used. All animals were fed the same adequate diet *ad lib.* The results are shown in Chart I. Each curve represents a group of six animals. Injections and weighings were done daily. The controls received 1 cc. of warm water; the thyroxine and new substances were injected as sodium salts in 1 cc. of warm water. The dosage of thyroxine was 0.05 mg. per animal per day, that of the new compounds 2 mg. per animal per day. The injections were given intraperitoneally.

Since the animals tested with the new substances, although not gaining weight quite as rapidly as the untreated controls, showed no effects comparable to the thyroxine controls, and since the molecular dosage of new substances was about thirty times that of thyroxine, it seems safe to conclude that there is very little, if any, thyroid activity in either of the new compounds.

The synthetic procedure was similar to that followed by Harington and Barger[2] for thyroxine. The only new steps introduced were the following



A 20% solution of 3,5-diiodo-4-(4′-methoxyphenoxy)-benzene diazonium chloride in glacial acetic acid was pre-

(2) Harington and Barger, *Biochem. J.*, **21**, 169 (1927).