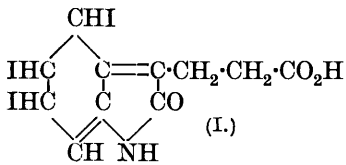
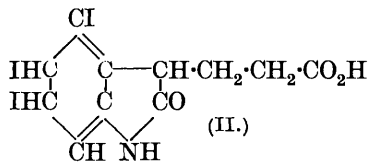
LXXXVII.—*Tautomerism in the Thyroxin Molecule.*

By CEDRIC STANTON HICKS.

IN a previous paper (J., 1925, **127**, 771) a possible relationship between thyroxin and tryptophan was shown, and the evidence pointed to the existence of a benzene nucleus in the substance, which was incompatible with almost complete hydrogenation of the aromatic fragment as postulated by Kendall (*J. Biol. Chem.*, 1919, **40**, 268). He has recently proposed (Chandler Lecture, Univ. Columbia, May, 1925) a modification (II) of his original formula (I), in support of which he offers further experimental proof.



(I.)



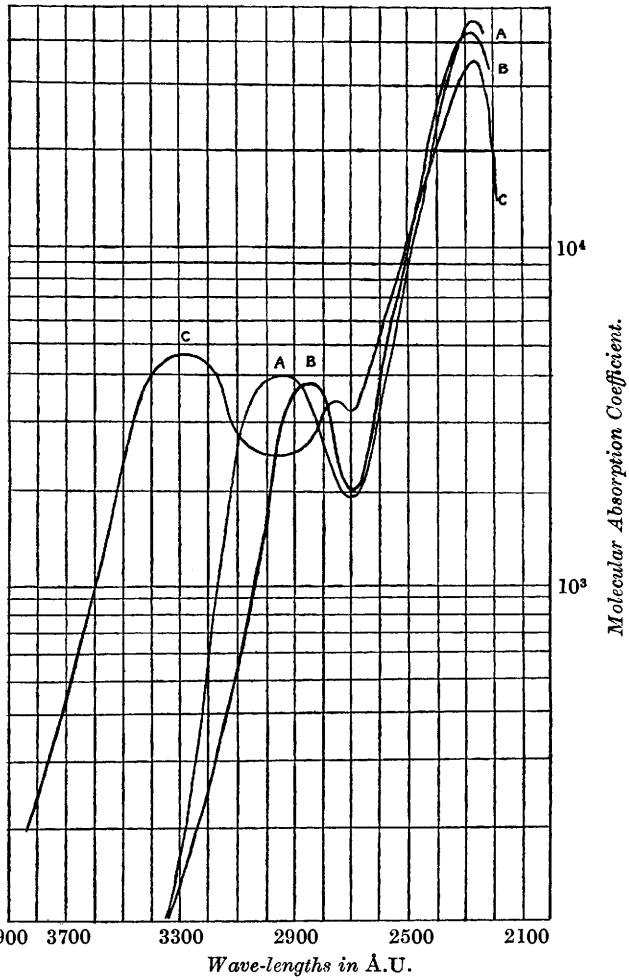
(II.)

A keto-enol type of tautomerism involving the lactim hydrogen is possible, and it was shown in the original work (*loc. cit.*) that the acetyl derivative did not produce the remarkable physiological effect of increase in heat production, when administered to the living organism. Kendall considers this enol transformation to be an intrinsic part of the mechanism whereby the molecule produces the

physiological effect, and further absorption spectrum study was undertaken to investigate this important phase of the subject.

Acetylthyroxin was prepared by Kendall's method (*loc. cit.*) from 20 mg. of commercial thyroxin. It remained amorphous and gummy,

FIG. 1.



A, keto-*Thyroxin.* B, *Acetylthyroxin.* C, *Thyroxin in alkaline solution.*

despite attempts to purify it by crystallisation from alcohol. Through the courtesy of Dr. Kendall, who specially prepared a specimen of the acetyl derivative from pure thyroxin, measurements of the absorption were made possible. The substance was dissolved

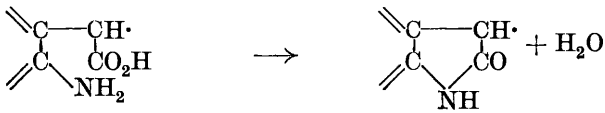
in 75% aqueous alcohol and examined in concentrations of $M/2{,}000$, $M/8{,}000$, $M/20{,}000$, $M/50{,}000$, and $M/100{,}000$.

keto-Thyroxin was prepared by dissolving the pure substance in 75% alcohol containing four equivalents of hydrochloric acid, and measurements were made at the same concentrations as the above.

The alcohol-soluble derivative obtained by passing carbon dioxide into a solution containing thyroxin and its equivalent of sodium hydroxide (*loc. cit.*) was dissolved in the minimum of 60% alcohol, and measurements were made as rapidly as possible at concentrations of $M/4{,}000$, $M/20{,}000$, $M/80{,}000$, and $M/100{,}000$.

Discussion.

Allowance must be made for the error in the value of the absorption coefficient likely to arise from the use of such minute quantities of material, but even so the evidence of the wave-lengths of the absorption bands remains. The curves for the acetyl derivative and the keto-form of thyroxin are more closely related to each other than to the curve for thyroxin in alkaline solution. The major band in the last lies at 3275 Å.U., whilst in the other two it lies respectively at 2850 Å.U. and 2925 Å.U., the third band at 2750 Å.U. being absent from both. The curve for the so-called open-ring form, prepared by the action of carbon dioxide on an alkaline solution of thyroxin, is almost identical with that for the *keto*-form, except that it tails off suddenly at 2400 Å.U., in the region of $\log \epsilon = 4$, into the Schumann region, giving no band as in the other cases. It is possible that during the time taken to make the measurements, even in dilute alcohol, water may be removed, with consequent closure of the ring, and therefore the results obtained may be intermediate values. The change is represented as follows :



Since the original measurements were made on thyroxin, Friedli has confirmed the presence of the band in indole, in the region 2100 Å.U. (*Bull. Soc. chim. Biol.*, 1924, **6**, 10, 908).

My thanks are due to Professor Sir F. Gowland Hopkins for his continued interest in the work, and to Dr. E. C. Kendall for the gift of acetylthyroxin. This work was done during the tenure of a Beit Memorial Fellowship for Medical Research.

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CAMBRIDGE. [*Received, December 8th,* 1925.]