134. *An Oxidation Product of Adrenaline.*

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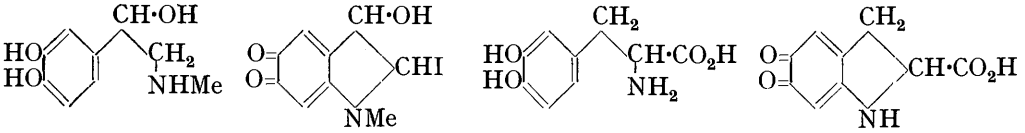
Adrenaline gives a deep red coloration when an aqueous solution is treated with potassium iodate solution (Fränkel and Allers, *Biochem. Z.*, 1909, **18**, 40; Kraus, *ibid.*, 1909, **22**, 131). The reaction has been used in histological work for staining tissues containing adrenaline and for the colorimetric estimation of adrenaline. A similar red coloration is given with a number of other oxidising agents and in the oxidation catalysed by tissue extracts (Green and Richter, *Biochem. J.*, in the press), but the oxidation products are very unstable and nothing is known of their chemical nature.

The red product formed when adrenaline (I) is oxidised with potassium iodate has now been isolated and found to have the properties of 2-iodo-3-hydroxy-1-methyl-2 : 3-dihydroindole-5 : 6-quinone (II).

The ring closure to give an indole derivative on oxidation in dilute aqueous solution can be compared with the ring closure which Raper found to take place under similar

conditions with dihydroxyphenylalanine (III) (*Biochem. J.*, 1927, **21**, 89). The product was in this case the dihydroindolequinone-2-carboxylic acid (IV).



(I.) (II.) (III.) (IV.)

Experimental.

l-Adrenaline (50 mg.) in 1 c.c. of 2% acetic acid was treated with 2 c.c. of 4% potassium iodate solution. The mixture went deep red and the product (75 mg.) slowly separated in prisms with a green metallic glance. Back titration of the excess of iodate showed that 57 mg. of potassium iodate were used in the reaction (calc. for 1 mol. per mol. of adrenaline, 58 mg.). The solution contained no iodide at the end of the reaction. A reaction was therefore indicated according to the equation

$$C_9H_{13}O_3N,CH_3{\cdot}CO_2H + KIO_3 \longrightarrow C_9H_8O_3NI + CH_3{\cdot}CO_2K + 3H_2O$$

This formula for the reaction product was confirmed by microanalysis (Found: C, 36·3; H, 2·7; N, 4·8; I, 40·4. $C_9H_8O_3NI$ requires C, 35·4; H, 2·6; N, 4·6; I, 41·6%).

The substance was very unstable. In the crystalline condition it decomposed after a few weeks. On heating, it decomposed without melting at about 150°. It was only very sparingly soluble in water, sparingly soluble in alcohol, and insoluble in most other solvents. The aqueous solution decomposed rapidly on treatment with dilute acid or alkali or on boiling.

The red colour of the compound suggested that it was quinonoid. This was confirmed by the fact that it was easily reduced by sulphur dioxide or magnesium powder and acetic acid; the colourless phenolic product gave, with ferric chloride, the green colour, changing to red on addition of ammonia, which is characteristic of a catechol derivative. The phenolic compound was optically active; a 1·15% solution obtained by reducing the quinone with sodium sulphite gave $[\alpha]_D^{18°} = +154°$. This indicated that the oxidation had not affected the asymmetry of of the CH·OH group.

Both the red quinone and its reduction product were much less basic than adrenaline, being insoluble in 5% acetic acid. On warming with 5% hydrochloric acid, the substance decomposed, forming free iodine, which could be extracted with chloroform. The ease with which iodine was formed made it likely that the iodine was substituted in the side chain rather than in the benzene nucleus.

Examination of the ultra-violet absorption spectrum of the reduction product showed that it gave a maximum at approximately 3800 A. The spectrum in the 2000—4000 A. region was of a different type from that given by adrenaline and other catechol derivatives. Since the absorption spectrum in this region is determined largely by the nature and number of the substituents in the benzene nucleus, this indicated that substitution in the benzene nucleus had probably occurred.

Ball and Chen obtained evidence by means of potentiometric measurements that the primary product formed when adrenaline is oxidised by a number of different oxidising agents is generally the corresponding *o*-quinone (*J. Biol. Chem.*, 1933, **102**, 702). The formula $C_9H_8O_3NI$ contains two hydrogen atoms less than an iodinated *o*-quinone of adrenaline. That means that two hydrogen atoms have been removed in a reaction which rendered the nitrogen atom less basic and at the same time brought about a substitution in the benzene nucleus. The simplest explanation is that ring closure between the nitrogen atom and the benzene nucleus to give a dihydroindole derivative had occurred. *o*-Quinones are known to condense with amines to give red amino-quinones (Jackson and Koch, *Ber.*, 1898, **31**, 1459). An intramolecular condensation of the type suggested is therefore not improbable.

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