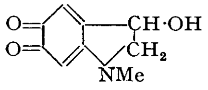
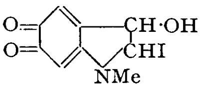
16. *The Oxidation of Adrenaline.*

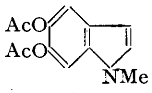
By F. Bergel and A. L. Morrison.

The oxidation of adrenaline and related compounds with oxygen and a catalyst or with potassium iodate has been studied and, in the case of adrenaline, after reductive acetylation, crystalline 5 : 6-*diacetoxy*-1-*methylindole* has been isolated.

Adrenaline and dihydroxyphenylalanine yield *o*-quinonoid indole derivatives when oxidised by catechol oxidase (Green and Richter, *Biochem. J.*, 1937, **31**, 596) or tyrosinase (Raper, *ibid.*, 1927, **21**, 89) and solutions of similar compounds were obtained in chemical oxidations of adrenaline by Fränkel and Allers (*Biochem. Z.*, 1909, **18**, 401), Kraus (*ibid.*, 1909, **22**, 131), and Green and Richter (*loc. cit.*). The product from the enzymatic oxidation of adrenaline is adrenochrome, probably (I). Richter and Blaschko (J., 1937, **601**) obtained the quinone (II) by oxidation of adrenaline with potassium iodate.


(I.)


(II.)


(III.)

In view of the probability that adrenochrome is the precursor of physiologically interesting substances, we some time ago reinvestigated the oxidation of adrenaline and related compounds. We oxidised them either catalytically in presence of palladium–charcoal (as an oxidase model) or repeated Richter and Blaschko's oxidation with potassium iodate.

Further evidence for the correct formulation of the quinone (II) was obtained when it was reductively acetylated with zinc and acetic anhydride and yielded 5 : 6-*diacetoxy*-1-*methylindole* (III), m. p. 100—101°. Reduction of (II) with sodium hydrosulphite, followed by acetylation, yielded 2-*iodo*-5 : 6-*diacetoxy*-1-*methylindole*, which on reduction with magnesium and acetic acid gave (III) with slightly higher m. p. than previously observed; the mixed m. p., however, showed no depression.

From the red solution obtained by catalytic oxidation of adrenaline when two molecular equivalents of oxygen were absorbed, adrenochrome could not be isolated but a brown melanin-like substance was gradually deposited. When, however, the red solution, before melanin formation, was reduced catalytically or with sodium hydrosulphite, and the resulting pale yellow solution acetylated, a very small amount of a crystalline compound, m. p. 105—110°, was obtained. It did not depress the m. p. of (III) and gave an analysis which fitted fairly well with the theoretical values for (III). We do not regard the identity of this substance with (III) as established, but in present circumstances further work on this subject cannot be undertaken.

No pure substance could be isolated from oxidations of 3 : 4-dihydroxyphenylethylamine and 3 : 4-dihydroxyphenylalanine.

Experimental.

2-*Iodo*-5 : 6-*diacetoxy*-1-*methylindole*.—Adrenaline (2 g.) was dissolved in 2% acetic acid (40 c.c.), and a 4% solution of potassium iodate (80 c.c.) added. After standing for 2 hours at 0°, the iodo-quinone formed was collected, washed with water, suspended in water, and shaken with ether and an excess of sodium hydrosulphite until it had been reduced and passed into solution. The aqueous portion was extracted five times with ether, and the combined extracts washed once with water, dried (sodium sulphate), and concentrated on the water-bath. Pyridine (20 c.c.) and acetic anhydride (60 c.c.) were added and the solution was left overnight at 0° and poured into ice-cold water. The precipitate, dried and recrystallised from methyl alcohol, had m. p. 153—155° (Found : I, 33·9; CH_3·CO, 23·3. $C_{13}H_{12}O_4NI$ requires I, 34·0; CH_3·CO, 23·1%).

5 : 6-*Diacetoxy*-1-*methylindole*.—(A) The iodo-quinone obtained as described above (0·75 g.), anhydrous sodium acetate (2 g.), zinc dust (2 g.), and acetic anhydride (40 c.c.) were refluxed for 1 hour. After cooling, the liquid portion was poured into ice-cold water and after some time this aqueous solution was extracted with ether. The extract was washed free from acid, dried, and concentrated. The residue was partly crystalline and after repeated recrystallisation from light petroleum (b. p. 100—120°) yielded 5 : 6-*diacetoxy*-1-*methylindole*, m. p. 100—101° (Found : C, 63·4; H, 5·2; N, 5·6. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

(B) 2-Iodo-5 : 6-diacetoxy-1-methylindole (0·5 g.) was dissolved in glacial acetic acid (10 c.c.), and magnesium (0·5 g.) gradually added, the temperature rising to about 60°. The mixture was heated on the water-bath until the magnesium had dissolved and was then poured into ice-cold water. The precipitated 5 : 6-diacetoxy-1-methylindole had m. p. 101—103°, not depressed by the specimen prepared in (A).

Catalytic Oxidation of Adrenaline and Reduction of the Product.—Adrenaline (0·5 g.) was suspended in water (50 c.c.), and acetic acid slowly added until the base dissolved and the *p*H was 4—5. 25% Palladium–charcoal (0·5 g.) was suspended in water and shaken with oxygen until absorption ceased. The solution of adrenaline acetate was added, and shaking with oxygen continued, 67 c.c. being absorbed after 3 hours. The dark red solution, on addition of some sodium hydrosulphite, became light yellow. It was cooled with ice and shaken with 4N-sodium hydroxide (10 c.c.) and acetic anhydride (4 c.c.). No solid separated, but ether extracted a small amount of a crystalline material, m. p. 105—110° after recrystallisation from light petroleum (b. p. 100—120°).

Hydrogenation of the deep red solution obtained by the oxidation of 1 g. of adrenaline with palladium as catalyst gave a yellow solution, 75 c.c. of hydrogen being taken up. When the cooled solution was shaken with acetic anhydride (15 c.c.) and 4% sodium hydroxide solution (20 c.c.), a solid separated in small amount, m. p. 105—110° after recrystallisation from light petroleum (b. p. 100—120°).

Mixtures of either of the above products with 5 : 6-diacetoxy-1-methylindole (m. p. 100—101°) melted at 100—110°.

Research Department, Roche Products Ltd., Welwyn Garden City. [*Received, September 5th*, 1942.]