THE CHEMISTRY OF THE AMINOCHROMES. PART VIII

THE PREPARATION AND PROPERTIES OF 4- AND 7-METHYLADRENOCHROME[1]

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ABSTRACT

Two new catecholamines, 2- and 5-methyladrenaline, have been prepared from 3-methylcatechol and they gave 4- and 7-methyladrenochrome, respectively, on oxidation. 7-Iodo-4-methyladrenochrome was obtained on oxidation of 2-methyladrenaline with potassium iodate; however, an iodoaminochrome could not be obtained in a similar manner from 5-methyladrenaline. The expected 5,6-dihydroxyindole derivatives were obtained on reduction of these aminochromes.

It has been known for many years that the oxidation of adrenaline with potassium iodate leads to the formation of deep-violet products (1, 2). The compound responsible for the violet color was first isolated in 1937 by Richter and Blaschko who described it as 3-hydroxy-2-iodo-1-methylindoline-5,6-quinone (i.e. 2-iodoadrenochrome) (3). However, it has recently been shown that iodination actually occurs in the 7-position of the adrenochrome nucleus and it was further demonstrated that iodination (and bromination) invariably occurs in the 7-position and not the 2-position in the aminochrome molecule (4).

As part of a research program into the chemistry of the aminochromes, that is being carried out in these laboratories, it was decided to prepare 2- and 5-methyladrenaline (I and II respectively) and to investigate the effects of the methyl substitution of the aromatic ring on the oxidation of these hitherto unknown catecholamines with several different oxidizing agents.

It was possible to prepare I and II by procedures similar to that originally described by Stolz for the preparation of adrenaline (5). ω-Chloro-3,4-dihydroxy-2-methylacetophenone (III) was prepared from 3-methylcatechol (IV) by a Friedel–Crafts condensation with chloracetyl chloride in the presence of aluminium chloride in carbon disulfide solution. Methylation of the phenolic hydroxy groups of III gave ω-chloro-3,4-dimethoxy-2-methylacetophenone (V), a compound that had previously been described in the literature (6), proving that the chloroacetyl residue had entered the aromatic ring of IV in the position ortho to the methyl group. The n.m.r. spectrum of III in hexadeuteroacetone showed two well separated doublets centered at δ 7.38 and δ 6.92 with a coupling constant of ca. 8.5 c.p.s., indicating the presence of two ortho aromatic hydrogens in the molecule and confirming the position of the chloroacetyl residue. ω-Methylamino-3,4-dihydroxy-2-methylacetophenone (VI) was prepared by treating III with methanolic methylamine at room temperature (cf. ref. 7). Treatment of III with sodium iodide in acetone gave 3,4-dihydroxy-ω-iodo-2-methylacetophenone (cf. ref. 6). Preliminary experiments indicated that there was no advantage in using the ω-iodo derivative to prepare VI. 2-Methyladrenaline (I) was obtained in good yield by catalytic hydrogenation of VI. The hydrochloride of I was hygroscopic, but the acid oxalate salt of I was not and was readily purified by recrystallization from aqueous ethanol.

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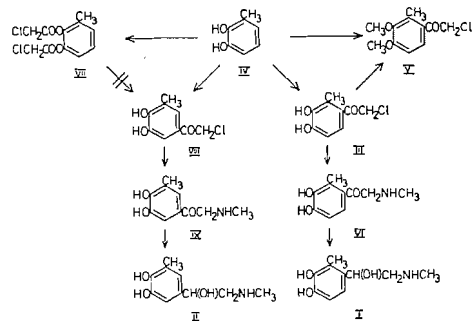
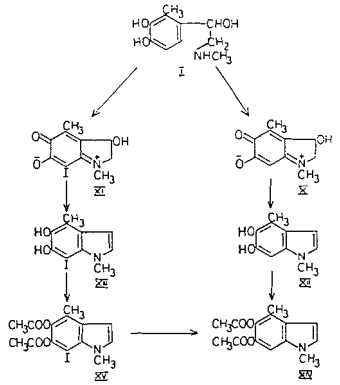


SCHEME 1.

The condensation of 3-methylcatechol (IV) with chloroacetyl chloride in boiling benzene, in the presence of phosphorus oxychloride (i.e. using conditions similar to those originally employed for synthesis of compounds of this type (cf. ref. 5, 8, 9), gave a chloroacetyl derivative of 3-methylcatechol, isomeric with, but different to, ω-chloro-3,4-dihydroxy-2-methylacetophenone (III), obtained by the conventional Friedel–Crafts procedure. This new ω-chloroacetophenone derivative was probably formed by a Fries rearrangement (cf. ref. 10) of an initially formed chloroacetyl ester of IV. In general this type of reaction can be carried out by either isolating a suitable ester of the catechol and subsequently rearranging it with either phosphorus oxychloride (9) or aluminium chloride (11), or by carrying out the entire procedure, without the isolation of the intermediate ester, in the presence of phosphorus oxychloride (9). In the present investigation, the latter procedure was employed. All attempts to bring about a direct Fries-type rearrangement of preformed 2,3-di(chloroacetoxy)toluene (VII) were unsuccessful. The n.m.r. spectrum of the second chloroacetophenone derivative in hexadeuteroacetone showed only a single peak (δ 7.5), corresponding to two hydrogens, in the aromatic proton region, effectively ruling out one of the two alternative structures, i.e., ω-chloro-2,3-dihydroxy-4-methylacetophenone, since the n.m.r. spectrum of this latter compound should indicate the presence of two ortho aromatic protons. Therefore, the only possible structure for this chloroactophenone derivative is ω-chloro-3,4-dihydroxy-5-methylacetophenone (VIII). 3,4-Dihydroxy-ω-methylamino-5-methylacetophenone (IX) was prepared by treatment of VIII with methanolic methylamine, and 5-methyladrenaline (II) was obtained by catalytic reduction of the aminoketone (IX). The hydrochloride, sulfate, and oxalate of 5-methyladrenaline (II) were prepared but were too hygroscopic to purify completely; however, it was possible to prepare a pure nonhygroscopic picrate of II.

4-Methyladrenochrome (X) was obtained as a deep-red crystalline solid on oxidation of 2-methyladrenaline (I) with silver oxide in dry methanol (cf. ref. 12); aqueous solutions of X were readily obtained by oxidizing the base (I) with potassium ferricyanide, buffered with sodium bicarbonate (cf. ref. 13). A crystalline monosemicarbazone of X could be prepared by standard procedures. 7-Iodo-4-methyladrenochrome (XI) was readily obtained as a violet-brown crystalline solid, when an aqueous solution of I was oxidized with potassium iodate.

5,6-Dihydroxy-1,4-dimethylindole (XII) was obtained on reduction of 4-methyladrenochrome (X) with ascorbic acid, and reduction of 7-iodo-4-methyladrenochrome (XI) with sodium borohydride gave 5,6-dihydroxy-7-iodo-1,4-dimethylindole (XIII); all attempts to reduce 7-iodo-4-methyladrenochrome (X I) with ascorbic acid, however, were



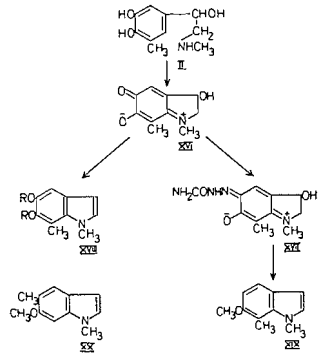
SCHEME 2.

unsuccessful. 5,6-Diacetoxy-1,4-dimethylindole (XIV) and 5,6-diacetoxy-7-iodo-1,4-dimethylindole (XV) were obtained on acetylation of XII and XIII respectively. Deiodination of XV with zinc and acetic acid gave XIV.

The red color of aqueous solutions of 4-methyladrenochrome (X) was discharged by alkali, with the formation of pale-yellow solutions, exhibiting the typical intense yellow green fluorescence associated with 5,6-dihydroxyindoxyls (see ref. 14 for references), indicating that the expected rearrangement of X to 4-methyladrenolutin had occurred. Treatment of an aminochrome with an acetic anhydride – pyridine mixture usually leads to the formation of a 3,5,6-triacetoxyindole derivative (cf. refs. 13, 15). However, solutions of 7-iodo-4-methyladrenochrome (XI) in acetic anhydride – pyridine mixtures did not lose their violet color, even after they had stood for several weeks at room temperature or had been heated at 80° for 2 h, suggesting that no reaction had occurred in this case.

7-Methyladrenochrome (XVI) was obtained as a dark violet, almost black, crystalline solid by the oxidation of 5-methyladrenaline (II) with potassium ferricyanide, in aqueous solution; it could also be prepared, in relatively poor yield, by the oxidation of II by silver oxide in methanol. The properties of the aminochrome (XVI) are unusual in several respects. The low water-solubility of XVI is unusual for non-halogenated aminochromes; aqueous solutions of XVI are violet, and not red in color, showing visible absorption maxima at 534 mμ in water and at 530 mμ in methanol, i.e. at longer wavelengths than are usual for unhalogenated aminochromes (cf. refs. 14, 15, 16). This shift of the visible absorption maxima towards longer wavelengths appears to be associated with 7-substitution. All known 7-halogenoaminochromes absorb in the 530 mμ region (cf. ref. 14). Two other 7-methyl substituted aminochromes have been described; solutions of 7-methyldopachrome and 4,7-dimethylnorepinochrome were prepared by Cromartie and Harley-Mason, and were reported to be deep violet in color (17). It was not possible to prepare an iodo derivative of XVI by the oxidation of II with potassium iodate under a wide variety of conditions; the iodine-free aminochrome (XVI) was invariably obtained. It would appear, therefore, that when the 7-position of the aminochrome nucleus is blocked the iodine atom will not enter any of the alternative free positions in the molecule.

The violet color of aqueous solutions of XVI was also discharged by alkali; yellow fluorescent solutions, presumably containing the corresponding 5,6-dihydroxyindoxyl, were obtained. 5,6-Dihydroxy-1,7-dimethyindole (XVIII: R = H), was obtained on the reduction of 7-methyladrenochrome (XVI) by ascorbic acid; this 5,6-dihydroxyindole



SCHEME 3.

derivative oxidizes readily in air, and was converted to its more stable diacetyl derivative (XVIII: R = CH_3CO).

The n.m.r. spectra of the three 5,6-diacetoxyindole derivatives (in deuterochloroform solution) described above (i.e. XIV, XV, and XVIII: R = CH_3CO) are fully compatible with the structures assigned to them on other grounds. The n.m.r. spectrum of 5,6-diacetoxy-1,4-dimethylindole (XIV) exhibited a singlet peak at δ 6.95, corresponding to the aromatic hydrogen in the 7-position; the hydrogens in the 2- and 3-positions of the indole nucleus in XIV gave rise to two doublets centered at δ 6.96 and δ 6.43 respectively, with a coupling constant of ca. 3 c.p.s. In the case of 5,6-diacetoxy-1,7-dimethylindole (XVIII: R = $COCH_3$), the 4-hydrogen was observed as a singlet at δ 7.19; the 2- and 3-hydrogens gave rise to two doublets centered at δ 6.89 and δ 6.35 respectively with a coupling constant of ca. 3 c.p.s. As would have been expected the n.m.r. spectrum of 5,6-diacetoxy-7-iodo-1,4-dimethylindole (XV) only showed two doublets, due to the 2- and 3-hydrogens, centered at δ 6.96 and δ 6.38 respectively, with a coupling constant of ca. 3 c.p.s. The positions (δ values) of the signals (and the coupling constants) due to the various hydrogen atoms in these substituted indole nuclei are quite compatible with what would have been expected from a consideration of the literature on the n.m.r. spectra of indoles (cf. refs. 4, 18, 19, 20).

5-Methyladrenaline (II) has two positions ortho to the ethanolamine side chain at which intramolecular cyclization might occur during aminochrome formation. However, theoretical considerations and consideration of all reported aminochrome cyclizations suggest that cyclization would occur at the 6-position (after the initial oxidation of the catocholamine to an uncyclized *o*-quinone derivative). If the cyclization occurred in the above manner a normal aminochrome (i.e. 7-methyladrenochrome (XVI)) would result. However, if cyclization had taken place at the 2-position in II, an abnormal aminochrome with the *o*-quinone function in the 6,7-position of the indole ring system would have resulted. To show that abnormal cyclization had not occurred, the monosemicarbazone (XVII) obtained from this aminochrome was treated with hot aqueous alkali, a procedure known to remove the semicarbazide residue from adrenochrome monosemicarbazones (21). The n.m.r. spectrum of the degradation product demonstrated that it was derived from 7-methyladrenochrome (XVI), since the degradation product was clearly 6-methoxy-1,7-dimethylindole (XIX). If abnormal cyclization had occurred during the aminochrome formation from II, the final product would have been 6-methoxy-1,5-dimethylindole (XX). The n.m.r. spectra of the degradation product (i.e. 6-methoxy-1,7-dimethylindole

(XIX)) in carbon tetrachloride and deuterochloroform both clearly show the presence of two aromatic hydrogens in an ortho relationship to each other. These aromatic hydrogen peaks are observed as doublets with a coupling constant of ca. 8.5 c.p.s. In the alternative structure (i.e. XX) the two hydrogens would be in a para relationship to each other and would not be expected to show a coupling constant of this magnitude. The δ values obtained are given in Table I.

TABLE I

Nuclear magnetic resonance spectral data for 6-methoxy-1,7-dimethylindole*

	Values of δ			
Solvent	4-H	5-H	2-H	3-H
CCl_4	7.16	6.62	6.62	6.16
$CDCl_3$	7.35	6.79	6.81	6.33

*All peaks are doublets; the δ values are calculated from the observed doublets.
The coupling constants observed for the 4- and 5-hydrogens are ~8.5 c.p.s. and those for the 2- and 3-hydrogens are ~3.2 c.p.s.

EXPERIMENTAL

Unless otherwise stated the infrared spectra were recorded on a Beckman IR-8 recording spectrophotometer; the ultraviolet and visible absorption spectra were recorded on a Unicam SP.800 recording spectrophotometer and the nuclear magnetic resonance spectra were recorded on either a Varian A-60 or HA-100 instrument. Only the more important peaks in the infrared and nuclear magnetic resonance spectra of certain compounds, which are relevant to the discussion, are reported.

The light petroleum used throughout this investigation was B.D.H. AnalaR grade (b.p. 80–100°). Peroxide-free ether was invariably used to minimize loses of readily oxidizable indole derivatives.

ω-Chloro-3,4-dihydroxy-2-methylacetophenone (III)

Powdered anhydrous aluminium chloride (50 g) was added cautiously, with stirring, to a solution of 3-methylcatechol[4] (25 g) and chloroacetyl chloride (20 g) in carbon disulfide[5] (300 ml), at 10°, with the rigorous exclusion of moisture. The resulting suspension was boiled, under reflux, until the evolution of hydrogen chloride had virtually ceased (ca. 45 min). Ice water (1 000 ml) and concentrated hydrochloric acid (50 ml) were added cautiously to the reaction mixture after it had been allowed to cool to room temperature. The crude product which separated out as an "off-white" solid was removed by filtration, washed with water, and on recrystallisation from water gave ω-chloro-3,4-dihydroxy-2-methylacetophenone (24 g) in colorless needles, m.p. 178°, ν_{max}^{Nujol} 3 480; 3 340; 1 665 cm^{-1}. The n.m.r. spectrum of III in acetone-d_6 showed signals at δ 7.38 (doublet) and δ 6.92 (doublet); J = 8.5 c.p.s.

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.96; H, 4.55; Cl, 17.22. Found: C, 54.16; H, 4.51; Cl, 18.08.

ω-Chloro-3,4-dimethoxy-2-methylacetophenone (V)

A solution of ω-chloro-3,4-dihydroxyacetophenone (1 g) and dimethyl sulfate (1.25 g) in acetone (30 ml) containing anhydrous potassium carbonate (1.4 g) was stirred and boiled under reflux for 8 h. After this time the suspension was poured into water (150 ml), and the aqueous reaction mixture was cooled to 5°. The crude crystalline product was removed by filtration, washed with water, and recrystallized from benzene – light petroleum. It gave ω-chloro-3,4-dimethoxy-2-methylacetophenone in colorless prisms (0.8 g), m.p. 101°, undepressed on admixture with an authentic sample, prepared by the method of Hornbaker and Burger (6). These two samples of this compound also had identical infrared spectra.

3,4-Dihydroxy-ω-iodo-2-methylacetophenone

A solution containing ω-chloro-3,4-dihydroxy-2-methylacetophenone (2 g) and sodium iodide (1.7 g) in acetone (250 ml) was stirred, at room temperature, for 30 min. After this time the solution was filtered, and the filtrate was evaporated to dryness. 3,4-Dihydroxy-ω-iodo-2-methylacetophenone (1.8 g) was obtained in pale-yellow needles, m.p. 171–172°, on recrystallization of the residue from aqueous ethanol.

Anal. Calcd. for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 37.17; H, 3.11.

[4]*Obtained from the Aldrich Chemical Co.*

[5]*Two other solvents: 1,2-dichloroethane and nitromethane, were tried in place of the carbon disulfide, to reduce the danger of fire, since the carbon disulfide system is very inflammable, but these alternate solvents gave unsatisfactory results.*

3,4-Dihydroxy-2-methyl-ω-methylaminoacetophenone (VI)

ω-Chloro-3,4-dihydroxy-2-methylacetophenone (4 g) was added in portions to a stirred, cooled mixture of methanol (5 ml) and a solution of methylamine (Matheson Co.) in methanol (15 ml, saturated at 5°); stirring was continued until solution was complete (ca. 5 min). The resulting brown solution was allowed to stand at 5° for 2 h, during which time tan-colored prisms of 3,4-dihydroxy-2-methyl-ω-methylaminoacetophenone (2.3 g), m.p. 218–222° (with decomposition) separated out, ν_{max}^{Nujol} 3 200 – 2 600; 1 630 cm^{-1}. It was not possible to purify this product by recrystallization since it does not dissolve in most of the common solvents.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 60.81; H, 6.72; N, 7.17.

The hydrochloride of 3,4-dihydroxy-2-methyl-ω-methylaminoacetophenone was prepared by stirring a suspension of the base in ethanol with excess concentrated hydrochloric acid; the base dissolved and colorless needles of 3,4-dihydroxy-2-methyl-ω-methylaminoacetophenone hydrochloride, m.p. 256° (with decomposition), separated out after the solution had been stirred at room temperature for a short time (ca. 5–15 min).

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.12; N, 6.08; Cl, 15.30. Found: C, 51.90; H, 5.95; N, 5.76; Cl, 15.20.

Treatment of a solution of ω-chloro-3,4-dihydroxy-2-methylacetophenone (0.5 g) in ether (50 ml) with methanolic methylamine (3 ml) for a few minutes at room temperature gave pale-yellow needles (0.3 g), m.p. 155°. This product, which is readily soluble in water and ethanol, is probably a phenolic methylamine salt of ω-chloro-3,4-dihydroxy-2-methylacetophenone[6] (cf. refs. 5, 22).

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.12; Found: C, 52.04; H, 6.24.

2-Methyladrenaline (I) Hydrogen Oxalate (i.e. 2-Methyl-α-methylaminomethylprotocatechuyl Alcohol Hydrogen Oxalate)

A suspension of 3,4-dihydroxy-2-methyl-ω-methylaminoacetophenone (5 g), oxalic acid dihydrate (3. 25 g), and 5% palladium–charcoal (3 g) in water (300 ml) at 40° was shaken in an atmosphere of hydrogen at atmospheric pressure for 30 h. After this time the reaction mixture was filtered, and the aqueous filtrate concentrated *in vacuo* (nitrogen "leak") to ca. 15 ml; colorless prisms of 2-methyladrenaline hydrogen oxalate (4.2 g) separated out after the concentrate had stood at room temperature overnight. A small sample of the product, purified for microanalysis by recrystallization from water, had m.p. 181° (with decomposition).

Anal. Calcd. for $C_{12}H_{17}NO_7$: C, 50.17; H, 5.97; N, 4.88. Found: C, 50.12; H, 6.11; N, 4.74.

2-Methyladrenaline (I) (Free Base)

A solution of 3,4-dihydroxy-2-methyl-ω-methylaminoacetophenone hydrochloride (3 g) in water (220 ml), containing 5% palladium–charcoal (1 g), was shaken in an atmosphere of hydrogen at atmospheric pressure for 8 h. The catalyst was removed by filtration and the clear filtrate was concentrated *in vacuo* (nitrogen "leak") below 40° to ca. 15 ml. Solid potassium carbonate (2 g) was added to the stirred solution; the crude base (2.6 g), which separated out after the reaction mixture had been allowed to stand at 5° for 1 h, was removed by filtration and was sufficiently pure for the next step in the synthesis of 4-methyladrenochrome. A sample of 2-methyladrenaline, purified for microanalysis by recrystallization from a large volume of methanol, was obtained in colorless prisms (m.p. 190–192° (with decomposition)).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.85; H, 7.82; N, 6.82.

4-Methyladrenochrome (X) (cf. the Preparation of Adrenochrome by the Method of Heacock et al. (12))

2-Methyladrenaline (1 g) was suspended in absolute methanol (30 ml), and 98% formic acid was added dropwise, with stirring, until a clear solution was obtained. Freshly prepared silver oxide was added in portions to the vigorously stirred solution. After being stirred, at room temperature for 3 min, the reaction mixture was filtered through a Dowex-1 (Cl^-) resin bed (cf. ref. 12). 4-Methyladrenochrome (0.11 g) was obtained in dark-red needles (totally decomposed without melting by 132°)[7] from the deep-red filtrate after it had been allowed to stand at −20° for 4 h. A second crop (0.06 g) of crystalline 4-methyladrenochrome was obtained by adding anhydrous ether (15 ml) to the remaining filtrate and keeping the solution at −20° overnight, $\lambda_{max}^{H_2O}$ 222, 312, 490 mμ; $\lambda_{max}^{CH_3OH}$ 221, 308, 484 mμ.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.82; N, 7.01.

4-Methyladrenochrome Monosemicarbazone

A solution of 2-methyladrenaline hydrochloride, prepared by suspending 2-methyladrenaline (0.2 g) in water (1.5 ml) and cautiously adding 2 *N* hydrochloric acid, with shaking, until all the solid had dissolved, was oxidized with a solution of potassium ferricyanide (1.15 g) and sodium bicarbonate (0.4 g) in water (3 ml). A deep-red solution of 4-methyladrenochrome formed rapidly and considerable frothing occurred (due to the evolution of carbon dioxide). After this solution had been allowed to stand at room temperature for 5 min, a solution containing semicarbazide hydrochloride (0.2 g) and sodium acetate (0.2 g) in water (1.5 ml) was added; the reaction mixture, after being stirred at room temperature for 10 min and standing at 5° for 5 h,

[6]*ω-Chloro-3,4-dihydroxy-2-methylacetophenone could be extracted with ether from aqueous solutions of the yellow product which had been made alkaline with sodium hydroxide.*

[7]*The decomposition points of all the aminochromes and aminochrome semicarbazones described in this paper were measured on a Leitz hot-stage instrument.*

deposited dark reddish-orange crystals of the crude semicarbazone. 4-Methyladrenochrome monosemicarbazone (0.125 g) was obtained in deep-orange needles (totally decomposed without melting by 248°) on recrystallization of the crude product from a pyridine–water (1.1) mixture.

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.95; H, 5.72; N, 22.44.

7-Iodo-4-methyladrenochrome (XI)

Potassium iodate (1.7 g) was added, at room temperature with stirring, to an aqueous solution of 2-methyladrenaline hydrochloride (prepared by cautiously adding 2 *N* hydrochloric acid to a suspension of 2-methyladrenaline (1 g) in water (350 ml) until a clear solution was obtained). The reaction mixture was stirred for 3 h at 5°; during this time deep-violet needles of 7-iodo-4-methyladrenochrome (1.1 g) separated out (totally decomposed without melting by ca. 110°), $\lambda_{max}^{H_2O}$ 234, 314, 534 mμ; $\lambda_{max}^{CH_3OH}$ 234, 309, 530 mμ.

Anal. Calcd. for $C_{10}H_{10}INO_3$: C, 37.64; H, 3.16; I, 39.78; N, 4.38. Found: C, 37.74; H, 3.15; I, 39.85; N, 4.45.

5,6-Dihydroxy-1,4-dimethylindole (XII)

Ascorbic acid was added in portions to a vigorously stirred two-phase system, consisting of an aqueous solution of 4-methyladrenochrome (prepared as described above by the oxidation of 2-methyladrenaline (0.3 g) with potassium ferricyanide) and ether (20 ml), until the red color of the aqueous phase had disappeared. The ether layer was separated and the aqueous phase was extracted with a further quantity of ether. Dry benzene (10 ml) was added to the combined, dried (Na_2SO_4) ether solutions, and the resulting solution was concentrated to ca. 5 ml *in vacuo* (nitrogen "leak"); colorless prisms of 5,6-dihydroxy-1,4-dimethylindole (0.11 g), m.p. 140–141°, were obtained by the addition of a small quantity of *n*-heptane to the warm concentrated benzene solution.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.56; H, 6.25; N, 7.87.

5,6-Diacetoxy-1,4-dimethylindole (XIV)

A mixture of dry pyridine (2 ml) and acetic anhydride (2 ml) was added to a dried ethereal solution of 5,6-dihydroxy-1,4-dimethylindole (prepared by the method described above). The light-brown solution, obtained after removal of the ether *in vacuo*, was allowed to stand overnight at room temperature and then poured into an ice–water mixture. The crude diacetate, that separated out, afforded colorless needles of 5,6-diacetoxy-1,4-dimethylindole (0.22 g), m.p. 135–136°, on recrystallization from benzene – light petroleum.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.79; N, 5.36. Found: C, 64.47; H, 5.82; N, 5.52.

5,6-Dihydroxy-7-iodo-1,4-dimethylindole (XIII)

Sodium borohydride was added cautiously to a vigorously stirred two-phase system, consisting of a suspension of 7-iodo-4-methyladrenochrome (0.5 g) in water (20 ml) and ether (20 ml), until the violet color of the aminochrome had been totally discharged. The ether layer was separated and the aqueous phase was extracted with a further quantity of ether. Dry benzene (10 ml) was added to the combined, dried (Na_2SO_4) ether extracts and the resulting solution was concentrated to ca. 5 ml *in vacuo* (nitrogen "leak"); colorless prisms of 5,6-dihydroxy-7-iodo-1,4-dimethylindole (0.19 g) were obtained by the addition of a small quantity of *n*-heptane to the warm concentrated benzene solution. This substance did not melt, but turned black somewhere between 140 and 180°, depending on the rate of heating.

Anal. Calcd. for $C_{10}H_{10}INO_2$: C, 39.62; H, 3.33; N, 4.62; I, 41.87. Found: C, 39.65; H, 3.24; N, 4.55; I, 42.04.

5,6-Diacetoxy-7-iodo-1,4-dimethylindole (XV)

A mixture of dry pyridine (2 ml) and acetic anhydride (2 ml) was added to a dried ethereal solution of 5,6-dihydroxy-7-iodo-1,4-dimethylindole, and the reaction mixture was worked up as described above. Colorless prisms of 5,6-diacetoxy-7-iodo-1,4-dimethylindole (0.22 g), m.p. 192–193°, were obtained on recrystallization of the crude product from benzene – light petroleum. The n.m.r. spectrum of this substance in deuterochloroform showed two doublets centered at δ 6.96 and δ 6.38 (J = 3.2).

Anal. Calcd. for $C_{14}H_{14}INO_4$: C, 43.43; H, 3.65; I, 32.79; N, 3.62. Found: C, 43.26; H, 3.72; I, 32.37; N, 3.57.

Deiodination of 5,6-Diacetoxy-7-iodo-1,4-dimethylindole (XV)

Zinc powder (0.8 g) was added in portions to a solution of 5,6-diacetoxy-7-iodo-1,4-dimethylindole in glacial acetic acid (5 ml). The suspension was boiled under reflux, with stirring, for 5 min and filtered, and the residual zinc was washed with a small quantity of hot glacial acetic acid. Crushed ice was added to the combined filtrate and washings and the resulting aqueous product was extracted several times with ether. The combined ether extracts were washed with aqueous sodium bicarbonate until free of acetic acid and finally with water. Dry benzene (5 ml) was added to the dried (Na_2SO_4) ether solution and the volume of the solution was reduced to ca. 3 ml. 5,6-Diacetoxy-1,4-dimethylindole (32 mg), identical in all respects with the sample prepared by the method described above, was obtained on the addition of a small quantity of light petroleum to the concentrated benzene solution.

2,3-Di(chloroacetoxy)toluene (VII)

A mixture of 3-methylcatechol (2 g) and chloroacetyl chloride (6 g) was heated in an oil bath at 120–130°, under anhydrous conditions, until hydrogen chloride evolution had ceased (i.e. ca. 90 min). The reaction mixture was poured into water (100 ml) and the product was stirred, at room temperature, for 30 min. The solid which precipitated after the aqueous product had been stored at 5° overnight gave colorless needles of 2,3-di(chloroacetoxy)toluene (3.8 g), m.p. 64°, on repeated recrystallization from aqueous ethanol, ν_{max}^{Nujol} 1 745, 1 770 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}Cl_2O_4$: C, 47.68; H, 3.63; Cl, 25.59. Found: C, 47.64; H, 3.81; Cl, 25.51.

ω-Chloro-3,4-dihydroxy-5-methylacetophenone (VIII)

A mixture of 3-methylcatechol (54 g), chloroacetic acid (47.3 g), pure phosphorus oxychloride[8] (28 g), and dry benzene was boiled, under reflux, in a nitrogen atmosphere, for 3½ h. Carbon tetrachloride (150 ml) was added and the reaction mixture allowed to stand overnight at 5°. The crude ω-chloro-3,4-dihydroxy-5-methylacetophenone (24 g), m.p. 178°, which separated as a pale-pink solid, was sufficiently pure for use in the next stage of the synthesis and was used directly, after washing with water and carbon tetrachloride. A sample was purified for analysis by recrystallization from water and had m.p. 180°, ν_{max}^{Nujol} 3 490, 3 290, 1 670 cm^{-1}. The n.m.r. spectrum of this substance in acetone-d_6 showed a single singlet peak (δ 7.5) in the aromatic hydrogen region.

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.96; H, 4.55; Cl, 17.72. Found: C, 53.87; H, 4.29; Cl, 17.85.

3,4-Dihydroxy-ω-iodo-5-methylacetophenone

3,4-Dihydroxy-ω-iodo-5-methylacetophenone (pale-yellow needles, m.p. 177°) was prepared from the corresponding chloro compound by a procedure identical to that described above for the preparation of the analogous 2-methylacetophenone derivative.

Anal. Calcd. for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 37.25; H, 3.38.

3,4-Dihydroxy-5-methyl-ω-methylaminoacetophenene (IX)

A mixture of methanol (5 ml) and a solution of methylamine in methanol (15 ml, saturated at 5°) was added at 0° to solid 3,4-dihydroxy-5-methyl-ω-chloroacetophenone (5 g), and the resulting suspension was shaken in a tightly stoppered flask for 6 min. Excess methylamine and the solvent was then removed *in vacuo*, below 90°; the brownish solid residue was triturated with ethanol (30 ml) and afforded tan prisms of 3,4-dihydroxy-5-methyl-ω-methylaminoacetophenone (2.1 g), m.p. 203–205°. The product, after filtration and washing with ethanol, was sufficiently pure for the next stage in the synthesis. A sample of IX was purified for analysis by recrystallization from a large volume of methanol and was obtained in light tan-colored prisms (m.p. 205–206° (with decomposition)).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.23; H, 6.87; N, 7.09.

3,4-Dihydroxy-5-methyl-ω-methylaminoacetophenone hydrochloride (colorless needles; m.p. 235°, with decomposition) was prepared from the base in an analogous manner to that described above for the preparation of the 2-methyl derivative.

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.12; N, 6.08; Cl, 15.30. Found: C, 51.86; H, 5.87; N, 5.94; Cl, 15.56.

Treatment of ω-chloro-3,4-dihydroxy-5-methylacetophenone with methanolic methylamine in ether, in a manner similar to that described above for the analogous 3-methyl compound, gave pale-yellow needles (m.p. 80°). The microanalytical values for carbon and hydrogen are not incompatible with this substance being a methylamine salt of ω-chloro-3,4-dihydroxy-5-methyl acetophenone (cf. refs. 5, 22).

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.12. Found: C, 52.19, H, 6.30.

5-Methyladrenaline (i.e. 5-Methyl-α-methylaminomethylprotocatechuyl Alcohol (II))

A solution of 3,4-dihydroxy-5-methyl-ω-methylaminoacetophenone hydrochloride (2.4 g) in water (200 ml), containing 5% palladium–charcoal (1 g), was shaken in an atmosphere of hydrogen at atmospheric pressure for 5 h. After this time the catalyst was removed by filtration and the clear filtrate was concentrated *in vacuo* (nitrogen "leak"), below 40°, to ca. 12 ml; solid potassium carbonate (1.5 g) was added, with stirring, and the crude base separated out, after the solution had been allowed to stand at 5° for 1 h. The product obtained in this manner was pure enough for oxidation directly to the corresponding aminochrome. A sample of 5-methyladrenaline was purified for microanalysis by recrystallization from a large volume of methanol and was obtained as colorless prisms, m.p. 195–197° (with decomposition).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.89; H, 7.84; N, 6.93.

5-Methyladrenaline picrate was prepared by adding a solution of picric acid (0.1 g) in dry benzene (8 ml) to a stirred suspension of the base (0.1 g) in ethanol (1 ml). The solid dissolved and dark-yellow needles of the

[8]*Commercial phosphorus oxychloride was purified by the procedure described by Ott (9), i.e. by washing a solution of the impure product in chloroform with ice water; removing the solvent in vacuo and fractional distillation of the product. The fraction boiling in the range 103–105° was collected and used directly. The direct use of the commercial product, which contains phosphorus pentachloride and phosphorus trichloride, leads to extensive tar formation and low yields of product.*

crude picrate were obtained after the solution had stood at 5° for 3 h. 5-Methyladrenaline picrate (0.12 g) m.p. 183°, was obtained in yellow needles on recrystallization of the crude product from a benzene–alcohol (9:1) mixture.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.26; N, 13.14. Found: C, 45.07; H, 4.32; N, 13.08.

7-Methyladrenochrome (XVI)

5-Methyladrenaline (0.6 g) was suspended in water (5 ml) and 2 *N* hydrochloric acid was added cautiously, with stirring, until a clear solution was obtained. A solution containing potassium ferricyanide (3.5 g) and sodium bicarbonate (1.2 g) in water (10 ml) was added, with stirring; the solution became deep violet in color and vigorous effervescence occurred. 7-Methyladrenochrome (0.18 g) (totally decomposed without melting by 105°) was obtained in deep violet (almost black) needles after the reaction mixture had been allowed to stand at 5° for 1 h, $\lambda_{max}^{H_2O}$ 232, 305, 534 mμ;

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.60; H, 5.72; N, 6.92.

Attempted Preparation of an Iodo-7-methyladrenochrome

An aqueous solution of 5-methyladrenaline hydrochloride (prepared from 0.3 g of the base) was treated with potassium iodate (0.5 g), at pH 7.2 (the pH of the solution was adjusted to 7.2 by the cautious addition of solid sodium carbonate), in an identical manner to that described above for the preparation of 7-iodo-4-methyladrenochrome. A deep-violet solution, having ultraviolet and visible spectral characteristics identical to those of 7-methyladrenochrome was obtained. The spectrum of the solution was not affected by prolonged reaction time (i.e. ca. 2 h), or by the addition of a further quantity of potassium iodate (0.5 g).

7-Methyladrenochrome monosemicarbazone (0.21 g) (totally decomposed without melting by 245°) was obtained, when a solution of semicarbazide hydrochloride (0.2 g) and sodium acetate (0.2 g) in water (3 ml) was added to a solution of 5-methyladrenaline hydrochloride that had been oxidized with potassium iodate. The sample of 7-methyladrenochrome monosemicarbazone, obtained in this manner, was identical to the product prepared by the method described below.

7-Methyladrenochrome Monosemicarbazone (XVII)

A solution of 7-methyladrenochrome, prepared by the oxidation of an aqueous solution of 5-methyladrenaline hydrochloride (from 1 g of base) with potassium ferricyanide, was treated with a solution of semicarbazide hydrochloride and sodium acetate in the manner described above for the analogous 4-methyl derivative. 7-Methyladrenochrome monosemicarbazone (0.95 g) (totally decomposed without melting by 245°) was obtained in wine-red needles on recrystallization of the crude product from a pyridine–water (1:1) mixture.

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.62; H, 5.61; N, 22.22.

5,6-Dihydroxy-1,7-dimethylindole (XVIII: R = H)

Ascorbic acid was added in portions, with stirring, to a two-phase system consisting of ether and an aqueous solution of 7-methyladrenochrome, prepared by the potassium ferricyanide oxidation of 5-methyladrenaline (0.6 g) by the method described above, until the deep-violet color of the solution had disappeared. The ether layer was removed and the aqueous phase was extracted with a further quantity of ether. Dry benzene (10 ml) was added to the combined, dried (Na_2SO_4) ethereal extracts, and the resulting solution concentrated to ca. 5 ml. Colorless prisms of 5,6-dihydroxy-1,7-dimethylindole (0.18 g) were obtained on addition of a small quantity of *n*-heptane to the warm benzene solution. The product could be further purified (m.p. 155°) by high vacuum sublimation at 160° (bath temperature) at 0.2 mm.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H,6.26; N, 7.91. Found: C, 67.64; H, 6.32; N, 7.87.

5,6-Diacetoxy-1,7-dimethylindole (XVIII: R = $COCH_3$)

A mixture of dry pyridine (3 ml) and acetic anhydride (3 ml) was added to a dry ethereal solution of 5,6-dihydroxy-1,7-dimethylindole, prepared by the method described above. The ether was removed *in vacuo*, and the concentrated reaction mixture was poured into an ice–water mixture, after it had been allowed to stand overnight at room temperature. Recrystallization of the crude product from benzene – light petroleum gave 5,6-diacetoxy-1,7-dimethylindole (0.35 g) in small colorless prisms, m.p. 137–138°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.79; N, 5.36. Found: C, 64.01; H, 5.68; N, 5.21.

6-Methoxy-1,7-dimethylindole (XIX): Prepared by the Alkaline Degradation of 7-Methyladrenochrome Monosemicarbazone and Subsequent O-Methylation (cf. ref. 21)

Solid potassium hydroxide (2 g) was added, with stirring, in a nitrogen atmosphere, to a suspension of 7-methyladrenochrome monosemicarbazone (0.5 g) in water (20 ml) at 90°, the resulting deep red-brown solution was boiled (in an atmosphere of nitrogen) until effervescence had ceased (ca. 2–5 min). The temperature of the solution was then reduced to ca. 50° by the addition of crushed ice; dimethyl sulfate (2.5 ml) was added dropwise and the reaction mixture was cautiously heated to 80°, and maintained at this temperature for 5 minutes. The resulting solution was cooled to room temperature and extracted several times with ether. The combined extracts were washed with *N* potassium hydroxide solution, dried (Na_2SO_4), and evaporated to dryness. The crude product was purified by recrystallization from light petroleum and

gave 6-methoxy-1,7-dimethylindole in colorless prisms (0.19 g); m.p. 93°: $\lambda_{max}^{C_2H_5OH}$ 224, 275, 292 (sh), 304 (sh) mμ. The significant n.m.r. peaks are given in Table I.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.55; H, 7.31; N, 7.98.

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