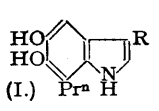
536. *The Chemistry of the Melanins. Part IV.* Some Dihydroxyindoles substituted in the Benzene Nucleus.*

By R. J. S. Beer, J. P. Brown, and Alexander Robertson.

5 : 6-Dihydroxy-7-*n*-propyl- and 5 : 6-dihydroxy-3-methyl-7-*n*-propyl-indole, together with compounds regarded as 5 : 6-dihydroxy-4-*n*-propyl- and 5 : 6-dihydroxy-3-methyl-4-*n*-propyl-indole, have been synthesised in continuation of studies on melanin formation. In their behaviour on autoxidation in faintly alkaline solution, these indoles resemble 5 : 6-dihydroxy-3-methylindole rather than 5 : 6-dihydroxyindole.

In a recent paper (*J.*, 1951, 703) Bu'Lock and Harley-Mason have elaborated a theory of melanin-formation from 5 : 6-dihydroxyindole by way of the corresponding *o*-quinone which is considered to undergo a self-condensation involving the 3- and the 7-positions. A test of the validity of this theory, it is stated, " would be provided by the investigation of the oxidation of a 5 : 6-dihydroxyindole substituted in the 7-position, which should not give a melanin." Two indoles of this type, *viz.*, 5 : 6-dihydroxy-7-*n*-propyl- (I; R = H) and 5 : 6-dihydroxy-3-methyl-7-*n*-propylindole (I; R = Me), and also two compounds believed to be 5 : 6-dihydroxy-4-*n*-propylindole (II; R = H) and its 3-methyl derivative (II; R = Me) were prepared in these laboratories in 1949.† The present communication deals with the synthesis and properties of these compounds.

The chief problem in the synthesis of dihydroxyindoles containing alkyl substituents in the benzene residue is the accessibility of suitable starting materials. Our primary objective was the preparation of 3-alkyl-4-amino- and 3-alkyl-5-amino-veratroles which were to be converted into 5 : 6-dihydroxyindoles by the method employed for the synthesis of 5 : 6-dihydroxy-3-methylindole (Part II, *J.*, 1949, 2061). *o*-Vanillin appeared to be a suitable starting material but, as this compound was not readily available in quantity, we decided to employ 6-*n*-propylguaiacol (III; R = H) which is easily obtained by rearrangement of *O*-allylguaiacol (Claisen and Eisleb, *Annalen*, 1913, **401**, 21) followed by hydrogenation with hydrogen and a palladium–charcoal catalyst (cf. Kurosawa, *Ber.*, 1915, **48**, 1603).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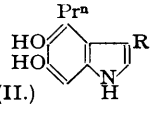
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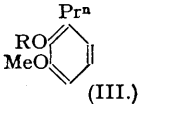
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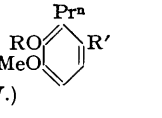
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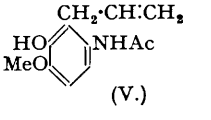
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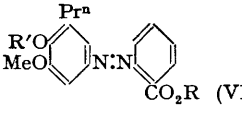
(VI.)

Although 3-methylveratrole on nitration gives 3-methyl-5-nitroveratrole in reasonable yield (Cain and Simonsen, *J.*, 1914, **105**, 156) it was found, in agreement with Kurosawa (*loc. cit.*), that 3-*n*-propylveratrole gave an intractable mixture of nitration products. 6-*n*-Propylguaiacyl acetate (III; R = Ac) also yielded a mixed product, but a pure mononitro-derivative, subsequently shown to be the 5-nitro-derivative (IV; R = Ac, R′ = NO_2), was separated by careful crystallisation. 4-Amino-3-*n*-propylveratrole was then obtained by successive deacetylation, methylation, and catalytic reduction. The base, which was extremely sensitive to aerial oxidation, was isolated as its hydrochloride and characterised by the formation of an acetyl derivative. The same 4-acetamido-3-*n*-propylveratrole was obtained by an independent route which, considered in conjunction with the above, serves to establish its orientation. 5-Nitroguaiacol (Paul, *Ber.*, 1906, **39**, 2773) was converted into 5-acetamidoguaiacol, the allyl ether of which yielded a *C*-allyl derivative (V) on Claisen rearrangement. This compound on methylation and catalytic reduction afforded an acetamido-*n*-propylveratrole identical with that already prepared. Attempts to effect a Claisen rearrangement with the allyl derivative of 5-nitroguaiacol were unsuccessful.

* Part III, *J.*, 1951, 2029.

† The syntheses of these indoles were described in a Thesis presented for the Degree of Doctor of Philosophy of this University by one of us (J. P. B.) in 1949.

4-Amino-3-*n*-propylveratrole was diazotised and condensed with ethyl α-acetylbutyrate, and the resulting oily red hydrazone cyclised to ethyl 5 : 6-dimethoxy-3-methyl-7-*n*-propylindole-2-carboxylate which, on hydrolysis, yielded the corresponding acid. Demethylation was effected with aluminium bromide in boiling toluene and the resulting 5 : 6-dihydroxy-3-methyl-7-*n*-propylindole-2-carboxylic acid, on decarboxylation, gave 5 : 6-dihydroxy-3-methyl-7-*n*-propylindole (I; R = Me). When ethyl α-acetylbutyrate was replaced by ethyl α-acetylpropionate in the initial Japp–Klingemann reaction, a similar sequence of reactions afforded ethyl 5 : 6-dimethoxy-7-*n*-propylindole-2-carboxylate, 5 : 6-dihydroxy-7-*n*-propylindole-2-carboxylic acid, and 5 : 6-dihydroxy-7-*n*-propylindole (I; R = H).

During explorative experiments, 5-*n*-propylvanillin was prepared, in low yield, from 6-*n*-propylguaiacol by application of the Reimer–Tiemann reaction, and also from 5-allylvanillin (Claisen and Eisleb, *loc. cit.*) by catalytic reduction. Methylation of 5-*n*-propylvanillin gave 5-*n*-propylveratraldehyde.

For the preparation of 5-amino-3-*n*-propylveratrole, diazotised methyl anthranilate was condensed with 6-*n*-propylguaiacol, and the resulting azo-compound (VI; R = Me, R′ = H) methylated and then hydrolysed to give the acid (VI; R = H, R′ = Me), a procedure which was more convenient than direct condensation with diazotised anthranilic acid followed by methylation. Hydrogenation of the azo-acid with the aid of a palladium catalyst furnished 5-amino-3-*n*-propylveratrole. This base which, unlike the isomeric 4-amino-3-*n*-propylveratrole, was relatively stable towards atmospheric oxygen, was then converted without difficulty into compounds regarded as 5 : 6-dihydroxy-4-*n*-propylindole (II; R = H) and 5 : 6-dihydroxy-3-methyl-4-*n*-propylindole (II; R = Me). In the synthesis of these compounds there is some ambiguity since the cyclisations may have led to 4 : 5-dihydroxyindole derivatives, but the normal cyclisation leading to 5 : 6-dihydroxyindoles is considered the more probable.

The behaviour of the four dihydroxyindoles on autoxidation in faintly alkaline solution has been studied qualitatively and is described in the Experimental section. All very rapidly form blue or violet precipitates which, in the case of 5 : 6-dihydroxy-7- and 5 : 6-dihydroxy-4-*n*-propylindole, become virtually black in a few hours. The blackening process is apparently very much retarded by the presence of the 3-methyl group in the other indoles.

It has now become clear that the rather crude methods used hitherto for comparison of the autoxidations are inadequate. Superficially, the behaviour of 5 : 6-dihydroxy-3-methylindole (Part II, *loc. cit.*) and of the indoles now described differs from that of 5 : 6-dihydroxyindole itself. Nevertheless, all these indoles give insoluble polymeric products and, although these polymers may well be of different types, in our opinion the differences are not at present sufficiently well-defined to warrant the construction of an elaborate theory of melanin formation. For this reason a more rigorous comparison of the behaviour of the various dihydroxyindoles on autoxidation, and also on enzymic oxidation, is in progress in these laboratories. The results of these studies will be reported later.

Experimental.

6-n-*Propylguaiacol*.—A solution of 6-allylguaiacol (20 g.) in methanol (200 ml.) was agitated with a palladium–charcoal catalyst in an atmosphere of hydrogen (room temperature and pressure) until the theoretical amount of hydrogen was absorbed (*ca.* 10 minutes). Purified by distillation, the product (b. p. 145°/25 mm.) was a colourless oil (19 g.) which, on being cooled, formed colourless needles, m. p. 15° (cf. Kurosawa, *loc. cit.*). 6-n-*Propylguaiacyl* p-*nitrobenzoate* separated from methanol in colourless prisms, m. p. 96° (Found : C, 64·5; H, 5·5; N, 4·7. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4; N, 4·4%).

O-*Acetyl*-5-*nitro*-6-n-*propylguaiacol*.—Acetylation of 6-*n*-propylguaiacol (20 g.) with acetic anhydride (20 ml.) and concentrated sulphuric acid (2 drops) during 1 hour gave the acetyl derivative (24·1 g.; b. p. 144°/20 mm.) which was purified by distillation. This product (3 g.), dissolved in glacial acetic acid (3 ml.) was treated with a solution of fuming nitric acid (5 ml.; *d* 1·5) in acetic acid (8 ml.) and, when the initial vigorous reaction had subsided, the red solution was poured into ice-water (75 ml.). The sticky solid, obtained by cooling the precipitated oil in a freezing mixture, was collected and crystallised from the minimum quantity of methanol giving the *nitro*-compound (1·2 g.) in very pale yellow prisms, m. p. 92° (Found : C, 56·7; H, 5·7; N, 5·4. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9; N, 5·5%). Nitration of larger batches of *O*-acetyl-6-*n*-propylguaiacol gave less satisfactory results.

5-*Nitro*-6-n-*propylguaiacol*.—*O*-Acetyl-5-nitro-6-*n*-propylguaiacol (12·3 g.) was heated on the steam-bath with a solution of sodium hydroxide (16 g.) in water (120 ml.) for 2 hours. On acidification, the resulting clear red solution deposited 5-*nitro*-6-n-*propylguaiacol* (10·7 g.) forming pale yellow needles, m. p. 77·5°, from 50% aqueous methanol, or colourless needles, m. p. 77·5°, from light petroleum (b. p. 60—80°) (Found : C, 56·8; H, 6·1; N, 6·4. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2; N, 6·6%).

4-*Nitro*-3-n-*propylveratrole*.—When 5-nitro-6-*n*-propylguaiacol (10·2 g.) was added to a solution of sodium hydroxide (4 g.) in water (10 ml.), the bright red sodium phenoxide separated. Methyl sulphate (12 ml.) was then added in portions (1 ml.) with vigorous shaking and, after addition of a further quantity of sodium hydroxide (4 g.) dissolved in water (10 ml.), the mixture was warmed on the

steam-bath for 30 minutes, cooled, and diluted with water (50 ml.). Crystallised from aqueous methanol, the yellow granular product (10·4 g.) gave 4-*nitro*-3-n-*propylveratrole* in long pale yellow needles, m. p. 40° (Found : C, 58·8; H, 6·7; N, 6·4. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7; N, 6·2%).

4-*Amino*-3-n-*propylveratrole*.—A solution of the foregoing nitroveratrole (5 g.) in methanol (100 ml.) was shaken in hydrogen with 20% palladium–charcoal for 2 hours, filtered, and evaporated, giving a purple oil which did not solidify. Since the aminoveratrole was very sensitive to oxidation, it was normally isolated as the hydrochloride (colourless plates, m. p. 195°, with previous darkening). A sample of the amine was converted in good yield into its *acetyl* derivative which formed silky colourless needles, m. p. 140°, from water (Found : C, 65·6; H, 7·9; N, 6·0. $C_{13}H_{19}O_3N$ requires C, 65·8; H, 8·0; N, 5·9%).

5 : 6-*Dimethoxy*-3-*methyl*-7-n-*propylindole*-2-*carboxylic Acid*.—The solution of the diazonium salt prepared from 4-amino-3-*n*-propylveratrole hydrochloride (5 g.), concentrated hydrochloric acid (15 ml.), water (50 ml.), and sodium nitrite (2 g.) was added immediately to a mixture of ethyl α-acetylbutyrate (Michael, *J. pr. Chem.*, 1905, **72**, 553) (4·5 g.) dissolved in 95% ethanol (50 ml.) at 0°, and sodium hydroxide (8 g.) dissolved in ice-water (12 ml.). After having been kept for 1 hour at 0°, the precipitated oily hydrazone was isolated with ether. A rapid stream of dry hydrogen chloride was passed through a solution of the crude hydrazone (7·2 g.) in dry ethanol (70 ml.) for 30 minutes. *Ethyl* 5 : 6-*dimethoxy*-3-*methyl*-7-n-*propylindole*-2-*carboxylate* was then isolated with ether after addition of water (200 ml.). Crystallised from 50% aqueous methanol (charcoal), this ester formed almost colourless needles (1·7 g.), m. p. 106° (Found : C, 66·7; H, 7·4; N, 4·7. $C_{17}H_{23}O_4N$ requires C, 66·9; H, 7·5; N, 4·6%), which gave a green Ehrlich reaction only on warming. The resinous 5 : 6-*dimethoxy*-3-*methyl*-7-n-*propylindole*-2-*carboxylic acid* obtained by hydrolysis of the ester (3 g.) for 1½ hours with boiling 10% alcoholic potassium hydroxide (60 ml.) was triturated with methanol and then crystallised from the same solvent, forming colourless needles (2·3 g.), m. p. 156—157° (Found : C, 64·9; H, 7·1; N, 5·3. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9; N, 5·1%).

5 : 6-*Dihydroxy*-3-*methyl*-7-n-*propylindole*.—A mixture of 5 : 6-dimethoxy-3-methyl-7-*n*-propylindole-2-carboxylic acid (0·5 g.), toluene (30 ml.), and aluminium bromide (2·85 g.) was heated under reflux for 25 minutes, cooled to 0°, and agitated with ice-cold dilute hydrochloric acid (50 ml.) and peroxide-free ether. The separated organic layer was combined with further ethereal extracts of the aqueous layer and evaporated, leaving a pearl-grey solid (0·25 g.), m. p. 190—192° (violent decomp.), which gave a deep green Ehrlich reaction at room temperature and a deep blue ferric reaction in water. It dissolved in very dilute aqueous sodium hydrogen carbonate to a blue solution which deposited a blue precipitate after *ca.* 10 minutes.

The crude dihydroxyindole acid (0·2 g.) was decarboxylated by distillation *in vacuo* (1 mm.); the air-bath temperature was raised from 120° to 200° during 10 minutes. The yellow glass which distilled, mainly at *ca.* 160°, partly solidified and after resublimation [120—130° (bath)/0·3 mm.] was crystallised from ligroin, giving 5 : 6-*dihydroxy*-3-*methyl*-7-n-*propylindole* in shining colourless prisms, m. p. 99—100° (Found : C, 70·3; H, 7·4; N, 6·9. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3; N, 6·8%). This indole, which darkens rapidly on exposure to air, gives a purple solution with a strong greenish-blue tinge in the Ehrlich test, and a blue precipitate with aqueous ferric chloride. In dilute aqueous sodium hydrogen carbonate, it forms a blue solution immediately which deposits a blue precipitate within 3 minutes. No further marked change was apparent even after several days. The freshly prepared blue precipitate dissolved momentarily in alcohol to a blue solution which rapidly deposited the pigment again in a highly insoluble form.

5 : 6-*Dihydroxy*-7-n-*propylindole*.—*Ethyl* 5 : 6-*dimethoxy*-7-n-*propylindole*-2-*carboxylate* (1·7 g.) was prepared from 4-amino-3-*n*-propylveratrole hydrochloride (5·1 g.) and ethyl α-acetylpropionate (3·5 g.) (Michael, *Ber.*, 1905, **38**, 2091) by the method described above for the 3-methyl derivative. The ester separated from a little methanol in stout prisms, m. p. 95—96° (Found : C, 66·2; H, 7·3; N, 5·0. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2; N, 4·8%), and gave a permanganate pink colour with hot Ehrlich's reagent. Hydrolysis with boiling 10% alcoholic potassium hydroxide furnished the corresponding *acid* (0·8 g.) which formed colourless prisms, m. p. 164°, from benzene (Found : C, 63·8; H, 6·3; N, 5·2. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). This acid (0·5 g.) was demethylated by the method used for its 3-methyl homologue, yielding 5 : 6-dihydroxy-7-*n*-propylindole-2-carboxylic acid (0·21 g.) as a pale grey amorphous solid, m. p. 180—182° (decomp.), which was decarboxylated directly by being heated *in vacuo* (170°/0·2 mm.) for 30 minutes. Crystallised from ligroin the resulting yellow glass (0·04 g.) gave 5 : 6-*dihydroxy*-7-n-*propylindole* in colourless needles, m. p. 106—107° (Found : C, 69·2; H, 6·8; N, 7·2. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). This indole resembles its homologue in giving a strong purple Ehrlich reaction and a blue-green ferric reaction with subsequent separation of a dark violet precipitate. The violet solution of the indole in dilute aqueous sodium hydrogen carbonate almost immediately deposits a blue-violet precipitate which darkens during a few hours.

5-*Acetamidoguaiacol*.—Reduction of 5-nitroguaiacol (Paul, *Ber.*, 1906, **39**, 2773) (3 g.), dissolved in methanol (50 ml.), with hydrogen (ordinary temperature and pressure) and 20% palladium–charcoal (1 g.) gave 5-aminoguaiacol, which was obtained as pale straw-coloured plates on evaporation of the filtered reaction mixture *in vacuo*. This base darkened rapidly on exposure to air and was, therefore, immediately acetylated with acetic anhydride (10 ml.) and water (30 ml.). Recrystallised from water (charcoal) the resulting 5-acetamidoguaiacol formed shining colourless prisms (2·1 g.), m. p. 171—172° (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2195, give m. p. 169—172°) (Found : C, 59·9; H, 6·3; N, 7·9. Calc. for $C_9H_{11}O_3N$: C, 59·7; H, 6·1; N, 7·7%).

5-*Acetamido*-6-*allylguaiacol*.—5-Acetamidoguaiacol (2 g.) in acetone (20 ml.) was heated under reflux for 5 hours with allyl bromide (3·5 ml.) and potassium carbonate (6 g.). The *allyl ether* (2·1 g.)

separated from water in fluffy colourless needles, m. p. 110° (Found: C, 65·0; H, 6·7; N, 6·4. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%). Rearrangement to 5-*acetamido*-6-*allylguaiacol* was effected by heating the ether (1·5 g.) initially to 170° and then raising the temperature to 250° during 10 minutes. The solidified melt was crystallised from 50% aqueous methanol and then from benzene, forming large pale pink needles (1·2 g.), m. p. 159° (Found: C, 65·3; H, 6·9; N, 6·1. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

4-*Acetamido*-3-n-*propylveratrole*.—Prepared from the foregoing guaiacol (1 g.) by the methyl iodide–potassium carbonate method, 4-*acetamido*-3-*allylveratrole* (1 g.) crystallised from a small volume of ether in colourless prisms, m. p. 140—141°, or from water in colourless needles, m. p. 141° (Found: C, 66·2; H, 7·4; N, 5·9. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 6·0%). Hydrogenation of this compound with the aid of a palladium–charcoal catalyst in methanol gave an almost quantitative yield of 4-acetamido-3-*n*-propylveratrole, obtained in colourless silky needles, m. p. 140°, undepressed by admixture with a sample prepared by the alternative route from 6-*n*-propylguaiacol; mixed with 4-acetamido-3-allylveratrole, m. p. 141°, it melted at 137—138°.

5-*Amino*-3-n-*propylveratrole*.—Methyl anthranilate (4 g.), dissolved in an ice-cold mixture of concentrated sulphuric acid (4 ml.) and water (20 ml.), was diazotised by addition of sodium nitrite (3 g.) in water (12 ml.). Fifteen minutes later the solution was added in a thin stream to a solution of 6-*n*-propylguaiacol (4 g.) in 10% aqueous sodium hydroxide (80 ml.) at 0°. After having been kept for 10 minutes the clear red solution was acidified and the precipitated azo-dye collected immediately (quantitative yield). Crystallised first from a little methanol and then from ligroin, *methyl* 4-*hydroxy*-3-*methoxy*-5-n-*propylazobenzene*-2′-*carboxylate* formed small orange prisms, m. p. 150—151° (Found: C, 65·8; H, 6·3; N, 8·9. $C_{18}H_{20}O_4N_2$ requires C, 65·9; H, 6·1; N, 8·5%). Methylation of the crude azo-compound (15 g.) by the methyl iodide–potassium carbonate method in boiling acetone for 12 hours gave the dimethoxy-ester as a red oil which was hydrolysed with boiling 5% methanolic potassium hydroxide for one hour. The resulting 3 : 4-*dimethoxy*-5-n-*propylazobenzene*-2′-*carboxylic acid* (9·4 g.) was crystallised from a little methanol and then from benzene, forming orange prisms, m. p. 111° (Found: C, 65·8; H, 6·3; N, 8·8. $C_{18}H_{20}O_4N_2$ requires C, 65·9; H, 6·1; N, 8·5%). Reductive fission of this azo-compound (5 g.) in methanol (100 ml.) with a palladium–charcoal catalyst and hydrogen at ordinary temperature and pressure gave 5-*amino*-3-n-*propylveratrole* (2·3 g.) which was precipitated from the concentrated reaction mixture by addition of 2N-sodium hydroxide solution and crystallised from light petroleum, forming clusters of almost colourless needles, m. p. 66·5° (Found: C, 67·4; H, 8·9; N, 7·2. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·7; N, 7·2%). The amine was more stable in air than 4-amino-3-*n*-propylveratrole. 5-*Acetamido*-3-n-*propylveratrole* formed colourless needles, m. p. 97°, from hot water (Found: N, 6·1. $C_{13}H_{19}O_3N$ requires N, 5·9%).

5 : 6-*Dimethoxy*-3-*methyl*-4-n-*propylindole*-2-*carboxylic Acid*.—Application of the Japp–Klingemann reaction to 5-amino-3-*n*-propylveratrole (4 g.) and ethyl α-acetylbutyrate (3·5 ml.) yielded a pure product (1·8 g.) regarded as *ethyl* 5 : 6-*dimethoxy*-3-*methyl*-4-n-*propylindole*-2-*carboxylate* in rosettes of colourless needles, m. p. 134—135° (from methanol) (Found: N, 4·7. $C_{17}H_{23}O_4N$ requires N, 4·6%). Hydrolysis of this ester with hot 10% alcoholic potassium hydroxide gave the corresponding *acid* (1·4 g. from 1·6 g. of ester) which crystallised from benzene in colourless plates, m. p. 189°, and with warm Ehrlich's reagent gave a bright blue colour (Found: C, 64·9; H, 7·0; N, 4·8. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9; N, 5·0%).

5 : 6-*Dihydroxy*-3-*methyl*-4-n-*propylindole*.—Demethylation of the foregoing acid (0·5 g.) with aluminium bromide (2·85 g.) in warm toluene (30 ml.) afforded 5 : 6-dihydroxy-3-methyl-4-*n*-propylindole-2-carboxylic acid (0·21 g.) as an off-white amorphous solid, m. p. 202° (decomp.). On decarboxylation by the standard procedure, the crude acid (0·2 g.) gave 5 : 6-*dihydroxy*-3-*methyl*-4-n-*propylindole* (0·15 g.) as a pale yellow oil which soon solidified. Crystallised from ligroin, it formed long colourless needles, m. p. 122° after sintering at 118°, which rapidly deteriorate on exposure to air (Found: C, 70·3; H, 7·4; N, 6·9. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3; N, 6·8%). The blue solution obtained by dissolving this indole in dilute sodium hydrogen carbonate solution deposited within 3 minutes a blue precipitate which slowly darkened in the course of several days. In the Ehrlich test transient violet and green colours were followed by a royal blue coloration.

5 : 6-*Dihydroxy*-4-n-*propylindole*.—Prepared from 5-amino-3-*n*-propylveratrole (3·5 g.) and ethyl α-acetylpropionate (3 ml.), *ethyl* 5 : 6-*dimethoxy*-4-n-*propylindole*-2-*carboxylate* (1·6 g.) crystallised from light petroleum in colourless needles, m. p. 133° (Found: C, 66·2; H, 7·3; N, 4·9. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2; N, 4·8%). On hydrolysis this ester (0·7 g.) yielded the corresponding *acid* (0·6 g.) which formed colourless triangular prisms, m. p. 162—164° (decomp.), from benzene (Found: C, 64·1; H, 6·7; N, 5·5. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). Demethylation of the acid (0·5 g.) under the usual conditions gave 5 : 6-dihydroxy-4-*n*-propylindole-2-carboxylic acid as a cream-coloured amorphous solid (0·36 g.), m. p. 206° (decomp.). This compound (0·2 g.) was decarboxylated by the standard method, affording 5 : 6-*dihydroxy*-4-n-*propylindole* as a pale yellow gum (0·15 g.) which rapidly solidified. Crystallised from a small volume of benzene, the indole formed short needles, m. p. 93—94° (Found: C, 69·0; H, 6·9; N, 7·0. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%), having a purple Ehrlich reaction. The blue solution obtained by dissolving the indole in dilute aqueous sodium hydrogen carbonate almost immediately deposited a violet precipitate which became virtually black in a few hours.

5-n-*Propylvanillin*.—(*a*) A mixture of 6-*n*-propylguaiacol (3 g.), alcohol (24 ml.), water (12 ml.), chloroform (3·5 ml.), and sodium hydroxide (9 g.) was heated under reflux for 1 hour. After removal of the chloroform and alcohol in a vacuum the aqueous residue was acidified with dilute sulphuric acid, giving 5-n-*propylvanillin* (0·6 g.), which was isolated with ether. Crystallised from light petroleum (b. p. 60—80°) this aldehyde formed almost colourless prisms, m. p. 56°, having a blue-green ferric reaction in alcohol (Found: C, 67·8; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%).

(*b*) 5-Allylvanillin (Claisen and Eisleb, *loc. cit.*) (4·1 g.), dissolved in methanol (100 ml.), was shaken with 20% palladium–charcoal (somewhat deactivated by having been kept in suspension in alcohol for 3 weeks) in hydrogen at ordinary temperature and pressure for 1 hour. Evaporation of the filtered solution and crystallisation of the product from light petroleum gave 5-*n*-propylvanillin as colourless prisms, m. p. and mixed m. p. 56°. Attempts to reproduce the conditions of this experiment, in particular the activity of the catalyst, were not entirely satisfactory and the yields varied widely.

5-n-*Propylveratraldehyde.*—Methylation of 5-*n*-propylvanillin (4 g.) with aqueous sodium hydroxide and methyl sulphate gave 5-*n*-propylveratraldehyde as a colourless oil (4·1 g.), b. p. 190°/50 mm., the *semicarbazone* of which separated from aqueous methanol in rosettes of colourless needles, m. p. 85° (Found: C, 58·7; H, 7·3; N, 15·8. $C_{13}H_{19}O_3N_3$ requires C, 58·9; H, 7·2; N, 15·8%).

O-*Allyl*-5-*nitroguaiacol.*—A mixture of 5-nitroguaiacol (7·5 g.), acetone (30 ml.), allyl bromide (12 ml.), and potassium carbonate (23 g.) was heated under reflux for 7 hours, diluted with water, and extracted with ether. The extracts were washed with alkali, dried, and evaporated, leaving the *allyl ether* which separated from light petroleum (b. p. 60—80°) in pale yellow cubes, m. p. 95° (Found: C, 57·3; H, 5·3; N, 6·3. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

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