INDOLE FORMATION BY OXIDATIVE CYCLIZATION

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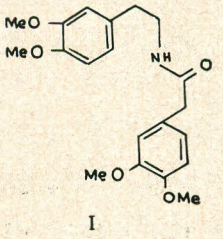
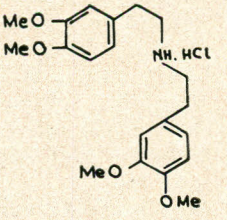
N, N′-Di-(3, 4-dihydroxyphenyl-β-ethyl) amine has been found to cyclise in presence of silver oxide to give N-(3, 4-dihydroxyphenyl-β-ethyl)-5, 6-dihydroxyindole which has been isolated as its tetra acetoxy derivative.

In a general study of possible oxidative cyclizations leading to the erythrina skeleton (VI), the amide (I) was subjected to the following sequence of reactions.

Homoveratryl homoveratroyl amide was prepared from homoveratric acid and homoveratrylamine, and was obtained as colourless needles, m.p. 126°. On reduction with lithium aluminium hydride it gave the corresponding amine which was crystallised as its hydrodrochloride, (II), m.p. 201°C.

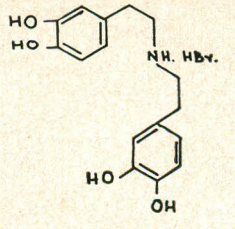


I

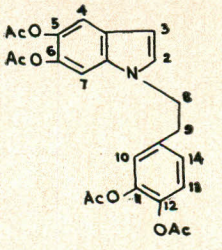


II

The N,N′-di-(3, 4-dimethoxyphenyl-β-ethyl)-amine was hydrolysed with 40% hydrobromic acid to give the phenol (III), m.p. 112-14°C. N,N′-di-(3,4-dihydroxyphenyl-β-ethyl)-amine, when stirred in oxygen-free dry pyridine or dry methanol suspension of freshly prepared equimolar amount of silver oxide under nitrogen gave a product which on acetylation gave a tetra-acetate (IV), m.p. 132-34°C. (or sublimed at 140°C./0.2 mm.).

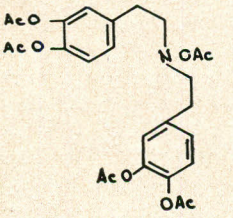


III



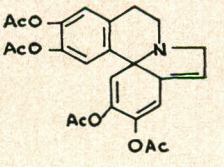
IV

The tetraacetate (IV) did not show any absorption at the amide carbonyl region in the infrared absorption spectra (no bands between 1600 to 1680 cm.-1). This showed a peak at 1570 cm.-1 (s) which is most probably due to the indole nucleus (indole showed peaks at 1585 and 1625 cm.-1). The original amine (III) on acetylation gave N,N′-di-(3,4-diacetoxyphenyl-β-ethyl)-acetamide (V), which sublimed at 180°C./0.2 mm. and showed three infrared bands as expected at 1770, 1650 and 1640 cm.-1 in chloroform solution.

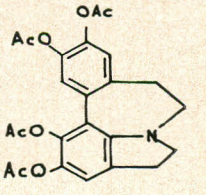


V

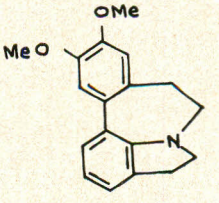
The presence of indole nucleus in the tetra-acetate (IV) could be confirmed through NMR spectra. The NMR spectra of N-(3,4-diacetoxyphenyl-β-ethyl)-5,6-diacetoxyindole (IV) (spectra taken in chloroform solution and the peaks given in p.p.m. relative to tetramethylsilane) showed the following peaks: singlet at 7.74 (acetates), triplet at 7.07 (H_2 at 9 position), triplet at 5.87 (H_2 at 8 position), doublet at



VI



VII



VIII

3.67 (H at 3 position) and amultiplet at 3.25-2.90 (six aromatic hydrogens at 2, 4, 7, 10, 13, 14). The doublet at 3.67 p.p.m. shows the presence of an indole nucleus.[1] The ultraviolet absorption data as given in Table 1 also conforms to a substituted indole type structure for this compound (IV) rather than any other structures, which would result if alternative ring closures took place to give the compound (VI) or (VII). The ultraviolet spectra of the compound (VIII) having a similar structure as (VII) are also different.

Experimental

Microanalyses were done by Alfred Bernhardt & Co., Bonn, W. Germany; melting points are uncorrected. Unless otherwise specified, ultraviolet spectra were taken in ethanol and infrared spectra of solids in potassium bromide pellet.

Homoveratroyl Homoveratric Amide.—Homoveratric acid (60 g.) was dissolved in dry benzene (400 ml.) and refluxed with thionyl chloride (60 ml.) under anhydrous conditions for 2 hours and left

TABLE 1.—ULTRAVIOLET SPECTRA.

Substance	Max. (mμ)*			ε		
Homoveratrylamine	285i; 204.	279;	230;	2,300; 32,500.	2,800;	3,600;
3, 4 - Dihydroxyphenyl - β - ethylamine hydrobromide	287i; 203	281; 202.	230;	2,300; 20,500.	2,800; 21,000.	6,200;
Homoveratrylhomoveratroylamide (I)	285i; 230.	280;	277i;	5,400; 17,300.	6,500;	6,300;
Homoveratrylhomoveratroyl amine hydrochloride (II)	285i; 229	280;	278i;	5,900; 22,000.	6,900;	6,800;
N, N′-Di-(3, 4-dihydroxyphenyl-β-ethyl)-amine (III) hydrobromide	283;	222.		9,500;	21,000.	
„ in basic solution	296;	245.		14,000;	14,900.	
N, N′-Di-(3, 4-diacetoxyphenyl-β-ehtyl)-acetamide (V)	272.5;	267i.		3,300;	2,700.	
„ in basic solution	311i; 261;	301; 256.	267;	7,800; 14,800;	9,100; 14,200;	13,400:
N - (3, 4 - diacetoxyphenyl - β - ethyl)-5,6 - diacetoxy-indole (IV)	296i;	287;	275i.	6,000;	6,900;	6,400;
„ in basic solution	320;	252.		7,700;	15,900;	
„ heated in acid solution	298i; 266;	282i; 260i.	272;	2,500; 6,500;	4,700; 4,500;	6,800;
Compound (VIII)	331; 247.	302;	268i;	1,800; 6,900;	1,900;	3,900 ;
Indole	287.5; 271;	279.5; 267i;	277. 216.5.	6,000; 7,500;	7,000; 7,000;	7,000; 40.500.

*In some cases lower wave length maxima have not been determined. This denotes inflexion.

overnight. The solvent was removed *in vacuo* and the acid chloride redissolved in dry benzene (200 ml.). Homoveratrylamine (70 g.) and dry pyridine (50 ml.) were dissolved in dry benzene (300 ml.) and the acid chloride solution was added to it with stirring. After two days chloroform was added to it and the organic layer washed with water and dilute hydrochloric acid followed by dilute caustic soda and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the amide crystallised from benzene-ether (81 g., 71%), m.p. 126°C.

Di - (3, 4 - dimethoxyphenyl - β - ethyl) - amine.—The above amide (25 g.) was dissolved in a mixture of dry tetra-hydrofuran (200 ml.) and dry dioxane (50 ml.), and slowly added to stirred refluxing slurry of lithium aluminium hydride (6.5 g.) in dry tetra-hydrofuran (350 ml.). After 18 hrs. of reflux, it was decomposed with water and filtered through celite and the latter washed with methanolchloroform mixture. The combined solvent was removed *in vacuo*. The residue was shaken with ether and dilute hydrochloric acid. The amine liberated from water was converted into its hydrochloride and crystallised from methanol-ether to give N,N′-di (3,4-dimethoxyphenyl-β-ethyl)-amine hydrochloride, m.p. 201°C. (Found: C, 62.65; H, 7.4; O, 16.85; N, 3.65; Cl, 9.55. $C_{20}H_{28}O_4NCl$ requires: C, 62.85; H, 7.4; O, 16.75; N, 3.65; Cl, 9.3). The hydrobromide had a m.p. of 208-9°C.

N,N′ - Di - (3, 4 - dihydroxyphenyl - β - ethyl) -amine hydrobromide.—The above tetramethoxyamine hydrobromide (5.2 g.) was refluxed under nitrogen with aqueous 40% hydrobromic acid (50 ml.) for 2 hrs. On cooling, the solution deposited some crystals which were filtered off, washed with a little cold water and crystallised from methanol-ether to give N,N′-di-(3,4-dihydroxyphenyl-β-ethyl)-amine hydrobromide (3 g.), m.p. 112-114°C. (Found: C, 49.6; H, 5.9; O, 20.95; N, 3.3; Br, 20.9; O-Me, 7.35. $C_{16}H_{20}O_4NBr.CH_3OH.\frac{1}{2}H_2O$ requires: C, 49.65; H, 6.15; O,21.4; N, 3.4; Br, 19.45; O-Me 7.55).

N,N′ - Di - (3, 4 - diacetoxyphenyl - β - ethyl) - acetamide.—The above amine hydrobromide (90 mg.) was dissolved in dry pyridine (2 ml.) and acetic anhydride (2 ml.) mixture and left at room temperature for 24 hours. After this period the solvents were removed *in vacuo* and the amide taken up in ether and washed with water. After removal of the solvent it was sublimed at 200°C./1 mm. of Hg. to give N,N′-di-(3,4-diacetoxyphenyl-β-ethyl)-acetamide. (Found: C, 62.6; H, 5.85; N, 3.4; O, 28.3; O-Acetyl, 25.55; O-Me, 0.00. $C_{26}H_{29}O_9N$ requires: C, 62.55; H, 5.85; N, 2.8; O, 28.8; O-Acetyl, 34.5; O-Me, 0.00).

N - (3,4 - diacetoxyphenyl - β - ethyl) - 5,6 - diacetoxy indole.—N,N′ - di- (3,4-dihydroxyphenyl-β-ethyl)—amine hydrobromide (0.5 g.) was dissolved in oxygenfree dry pyridine (100 ml.) and shaken with dry freshly prepared silver oxide (from 1.4 g. silver nitrate), under nitrogen for 3 hours. Sulphur dioxide solution in pyridine (3 ml. of 15% solution) was added to it followed by a drop of dilute sulphuric acid and it was then filtered through celite. The solvents were removed *in vacuo* and the brown mass acetylated with acetic anhydride (11 ml.) in pyridine (11 ml.) for 24 hours. The solvent was removed *in vacuo* and it was chromatographed through fluorocel and the substance collected (0.35 g.) was sublimed at 130°C. *in vacuo* which on crystallisation from benzene-ether-petroleum ether (60-80°C.) gave *N, (3,4-diacetoxyphenyl-β-ethyl)-5,6-diacetoxy indole*, m.p. 132-134°C., sublimed at 140°C./0.2 mm. (Found: C, 63.55; H, 5.00; N, 3.6; O, 28.45; O-Acetyl, 36.4; O-Me, 0.00. $C_{24}H_{23}O_8N$ requires: C, 63.55; H, 5.1; N, 3.1; O, 28.25; O-Acetyl, 38.0; O-Me, 0.00). The reaction when carried out in dry oxygen free methanol also gave similar results.

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References

1. Harley-Mason, J. Chem. Soc., 200 (1953).