

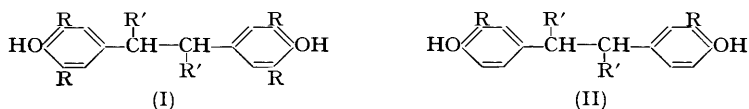
532. *Substitution Reactions of Hexæstrol and Analogous Compounds.*

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Halogenation of hexæstrol (*meso*-3 : 4-di-*p*-hydroxyphenylhexane) by sulphuryl chloride, bromine, or iodine, is shown to give predominantly the corresponding tetra-substituted derivatives, whereas nitration in acetic acid medium gives a dinitro-product. Similar results are recorded with higher homologues of hexæstrol, with 4 : 4'-dihydroxydibenzyl, and various 4 : 4'-dihydroxydiphenylmethanes. During this research, several *o*-aminophenols and benzoxazoles of the same series were prepared as potential tuberculo-static agents.

HEXÆSTROL (*meso*-3 : 4-di-*p*-hydroxyphenylhexane) is a readily available intermediate (cf. Buu-Hoï and Hoán, *J. Org. Chem.*, 1949, **14**, 1023) for the preparation of compounds built on the same molecular pattern as synthetic œstrogens, and with possible pituitary-inhibitory and antithyroid activity.

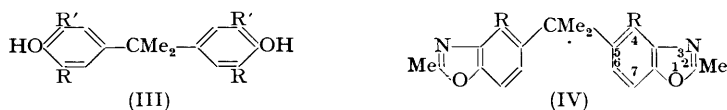
Halogenation reactions of hexæstrol have now been studied, as these should result in compounds bearing halogen atoms at 3 : 5-positions, as with tetrachloro- and tetrabromothyronine (Lerman and Harington, *J. Clin. Invest.*, 1948, **27**, 546; Richards, Brady, and Riggs, *J. Clin. Endocrinol.*, 1949, **9**, 1107) and other thyroxin analogues (cf. Wilkinson, Sheehan, and Maclagan, *Biochem. J.*, 1951, **48**, 188; **49**, 710, 714). Treatment of hexæstrol with sulphuryl chloride or bromine in excess readily gave 3 : 5 : 3' : 5'-tetrachlorohexæstrol



(I; R = Cl, R' = Et) and 3 : 5 : 3' : 5'-tetrabromohexæstrol (I; R = Br, R' = Et). 3 : 5 : 3' : 5'-Tetraiodohexæstrol (Oxley, Lowe, Peak, and Watkins, *J.*, 1951, 3288) was similarly obtained from iodine and yellow mercuric oxide. Homologues of hexæstrol reacted in the same way, 4 : 4'-dihydroxydibenzyl and *meso*-4 : 5-di-*p*-hydroxyphenyl-2 : 7-dimethyloctane giving the corresponding 3 : 5 : 3' : 5'-tetrahalogenated derivatives.

Nitration of hexæstrol in acetic acid medium afforded 3 : 3'-dinitrohexæstrol (II; R = NO<sub>2</sub>, R' = Et), and the same reaction was observed with its homologues such as 4 : 4'-dihydroxydibenzyl, *meso*-4 : 5-di-*p*-hydroxyphenyloctane and *meso*-4 : 5-di-*p*-hydroxyphenyl-2 : 7-dimethyloctane.

Hexæstrol and its homologues thus closely resembled 4 : 4'-dihydroxydiphenylmethanes, both in respect of halogenation (cf. Zincke and Grueters, *Annalen*, 1905, **343**, 86; Zincke and Goldemann, *ibid.*, 1908, **362**, 205; Auwers and Rietz, *ibid.*, 1907, **356**, 154) and of nitration (cf. Széky, *Chem. Zentr.*, 1904, **11**, 1737). From 2 : 2-di-*p*-hydroxyphenylpropane, Széki obtained 2 : 2-di-(4-hydroxy-3-nitrophenyl)propane (III; R = NO<sub>2</sub>,



R' = H), m. p. 133°, which was reduced by stannous chloride to a diamine of m. p. 218—219°; repetition of this experiment showed the m. p. of the dinitro-compound to be in accord with that of Széki's compound, but the diamine had m. p. 270°. Similar nitration of 2 : 2-di-(4-hydroxy-3-methylphenyl)propane (III; R = Me, R' = H) yielded the dinitro-product (III; R = Me, R' = NO<sub>2</sub>). No proof has previously been provided for the position of nitration of 4 : 4'-dihydroxydiphenylmethane, apart from analogy with *p*-cresol. The orientation has now been established by conversion of the diamine (III; R = NH<sub>2</sub>,

R' = H) into 2 : 2-di-(2-methyl-5-benzoxazolyl)propane (IV; R = H) by acetic anhydride; a similar compound (IV; R = Me) was obtained from the reduction product of 2 : 2-di-(4-hydroxy-3-methyl-5-nitrophenyl)propane. In view of the significant tuberculostatic activity of *o*-aminophenol (Jouin and Buu-Hoi, *Ann. Inst. Pasteur*, 1946, **72**, 580), the above amines are of interest as potential antitubercular agents, as also is 3 : 3'-diaminohexæstrol (II; R = NH<sub>2</sub>, R' = Et), prepared by reduction of the corresponding dinitro-compound. 3 : 5 : 3' : 5'-Tetrabromohexæstrol, kindly tested by Mrs. Pitt-Rivers (at the National Institute for Medical Research, London), showed no antithyroxine action as assayed by the method of goitre prevention in rats; 3 : 3'-diaminohexæstrol dihydrochloride has shown marked tuberculostatic activity *in vitro*, as was expected.

## EXPERIMENTAL

3 : 5 : 3' : 5'-Tetrachlorohexæstrol (I; R = Cl, R' = Et).—To a solution of recrystallised hexæstrol (m. p. 187°; 2 g.) in anhydrous chloroform (200 c.c.), sulphuryl chloride (6 g.) was added in small portions with stirring; the mixture was refluxed for 6 hr., the chloroform distilled off, and the solid residue recrystallised from acetic acid, giving the *tetrachloro*-compound (2.5 g.) as prisms, m. p. 203° (Found: C, 53.0; H, 4.4. C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>Cl<sub>4</sub> requires C, 52.7; H, 4.4%). Use of less sulphuryl chloride (3 g.) resulted in the same product after repeated crystallisation, the more soluble portions consisting of chlorine-containing substances melting over a wide range and of some recovered hexæstrol. The *dimethyl ether*, prepared from 3 : 5 : 3' : 5'-tetrachlorohexæstrol (0.5 g.), methyl iodide (0.4 g.), and potassium hydroxide (0.16 g.) in ethanol, formed needles, m. p. 183°, from ethanol (Found: C, 54.6; H, 5.2. C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>Cl<sub>4</sub> requires C, 54.8; H, 5.0%).

3 : 5 : 3' : 5'-Tetrabromohexæstrol.—To a solution of hexæstrol (4 g.) in acetic acid (400 c.c.), bromine (9.5 g. in acetic acid) was added in small portions with stirring; after 2 hr., water was added, and the solid precipitate collected, washed with water, and recrystallised from acetic acid, giving the *tetrabromo*-compound as needles (5 g.), m. p. 230° (Found: C, 37.0; H, 3.2. C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 36.9; H, 3.1%); an attempt to obtain 3 : 3'-dibromohexæstrol by using less bromine (4 g.) failed. The *dimethyl ether*, prepared as above, formed, from ethanol-benzene, needles, m. p. 211° (Found: C, 39.0; H, 3.6. C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 39.1; H, 3.6%).

3 : 5 : 3' : 5'-Tetraiodohexæstrol.—To a mixture of hexæstrol (4 g.), yellow mercuric oxide (13 g.), and ethanol (150 c.c.) was added pulverised iodine (15 g.) in small portions with shaking. After 1 hr., the solid was filtered off and washed with hot ethanol; the filtrate gave on dilution with water a precipitate, which was recrystallised first from acetic acid, then from ethanol, giving almost colourless prisms (5 g.), melting at 233°, solidifying again, then re-melting at 236°; Oxley *et al.* (*loc. cit.*) gave m. p. 239°. The *dimethyl ether* formed prisms, m. p. 206°, from ethanol-benzene (Found: C, 30.5; H, 2.9. C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>I<sub>4</sub> requires C, 29.9; H, 2.7%).

3 : 3'-Dinitrohexæstrol (II; R = NO<sub>2</sub>, R' = Et).—A fine suspension of hexæstrol (10 g.) in cold acetic acid (600 c.c.) was treated with nitric acid (*d* 1.33; 5.2 g. in acetic acid) in small portions with stirring; a clear solution was obtained, which soon deposited crystals of 3 : 3'-dinitrohexæstrol. After 1 hr. at room temperature, the precipitate was collected, washed with water, and recrystallised from acetic acid, giving pale yellow needles (10 g.), m. p. 233° (Found: C, 60.0; H, 5.7. C<sub>18</sub>H<sub>20</sub>O<sub>6</sub>N<sub>2</sub> requires C, 60.0; H, 5.6%).

3 : 3'-Diaminohexæstrol.—A suspension of the foregoing compound (11 g.) in ethanol (500 c.c.) was treated with a solution of stannous chloride (50 g.) in hydrochloric acid (70 c.c.) in small portions with stirring, and the mixture refluxed for 6 hr. The ethanol was distilled off, the residue treated with dilute aqueous ammonia to pH 3, and the precipitate filtered off and washed with water. The filtrate was treated with more ammonia to pH 7, and the precipitated *amine* collected, washed with water, dried, and recrystallised from ethanol, giving grey-tinged prisms (5 g.), m. p. 273° (darkening above 260°), soluble in hydrochloric acid or aqueous sodium hydroxide (Found: C, 71.6; H, 8.2; N, 9.0. C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>N<sub>2</sub> requires C, 72.0; H, 8.0; N, 9.3%).

meso-4 : 5-Di-(3 : 5-dibromo-4-hydroxyphenyl)-2 : 7-dimethyloctane (I; R = Br; R' = Bu<sup>t</sup>).—A solution of meso-4 : 5-di-(4-hydroxyphenyl)-2 : 7-dimethyloctane (4 g.; m. p. 207°), prepared according to Buu-Hoi and Hoán (*loc. cit.*), in acetic acid (400 c.c.) was treated with bromine (7.8 g.) in the usual way, giving a *product* which formed needles (5 g.), m. p. 210°, from acetic acid (Found: C, 41.3; H, 4.0. C<sub>22</sub>H<sub>26</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 41.1; H, 4.1%). The *dimethyl ether* crystallised from ethanol as prisms, m. p. 178° (Found: C, 43.4; H, 4.7. C<sub>24</sub>H<sub>30</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 43.0; H, 4.5%).

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meso-4 : 5-Di-(4-hydroxy-3-nitrophenyl)octane (II; R = NO<sub>2</sub>, R' = Pr<sup>n</sup>).—A solution of meso-4 : 5-di-*p*-hydroxyphenyloctane (2.5 g.; m. p. 168—169°) in acetic acid, treated with nitric acid (1.2 g.), yielded a compound (1.8 g.) crystallising from acetic acid as yellow prisms, m. p. 218° (Found : C, 61.8; H, 6.2. C<sub>20</sub>H<sub>24</sub>O<sub>6</sub>N<sub>2</sub> requires C, 61.8; H, 6.2%).

meso-4 : 5-Di-(4-hydroxy-3-nitrophenyl)-2 : 7-dimethyloctane (II; R = NO<sub>2</sub>, R' = Bu<sup>1</sup>).—From acetic acid this *phenol* formed yellow needles, m. p. 182° (Found : C, 63.3; H, 6.7. C<sub>22</sub>H<sub>28</sub>O<sub>6</sub>N<sub>2</sub> requires C, 63.5; H, 6.7%).

3 : 5 : 3' : 5'-Tetrabromo-4 : 4'-dihydroxydibenzyl (I; R = Br, R' = H).—4 : 4'-Dihydroxydibenzyl was prepared from 4-methoxybenzyl chloride by treatment with iron powder in aqueous medium (cf. Buu-Hoï and Hoán, *loc. cit.*), and demethylation of the resulting 4 : 4'-dimethoxydibenzyl with pyridine hydrochloride. A solution of 4 : 4'-dihydroxydibenzyl (4 g.) in acetic acid (300 c.c.) was treated with bromine (12 g. in acetic acid) in the usual way; the *product* (5.5 g.) crystallised as prisms, m. p. 195°, from acetic acid (Found : C, 31.6; H, 2.2. C<sub>14</sub>H<sub>10</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 31.7; H, 1.9%). The *dimethyl ether* formed needles, m. p. 191°, from ethanol (Found : C, 34.2; H, 2.6. C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>Br<sub>4</sub> requires C, 34.4; H, 2.5%).

4 : 4'-Dihydroxy-3 : 5 : 3' : 5'-tetraiododibenzyl (I; R = I, R' = H).—Prepared by Oxley's procedure (Oxley *et al.*, *loc. cit.*), this formed fine colourless prisms, m. p. 237°, from acetic acid (Found : I, 70.4. C<sub>14</sub>H<sub>10</sub>O<sub>2</sub>I<sub>4</sub> requires I, 70.8%). The *dimethyl ether* formed needles, m. p. 215°, from ethanol (Found : C, 25.4; H, 2.0. C<sub>16</sub>H<sub>14</sub>O<sub>2</sub>I<sub>4</sub> requires C, 25.7; H, 1.9%).

4 : 4'-Dihydroxy-3 : 3'-dinitrodibenzyl (II; R = NO<sub>2</sub>, R' = H).—An ice-cooled solution of 4 : 4'-dihydroxydibenzyl (3 g.) in acetic acid (300 c.c.) was treated with nitric acid in the usual way; the product crystallised as pale yellow needles, m. p. 198°, from acetic acid (Found : C, 55.0; H, 4.0. C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub> requires C, 55.3; H, 3.9%).

2 : 2-Di-(3-amino-4-hydroxyphenyl)propane.—2 : 2-Di-(4-hydroxy-3-nitrophenyl)propane (11 g.; m. p. 134°) was reduced by stannous chloride (45 g. in 70 c.c. of hydrochloric acid) as for 3 : 3'-diaminohexæstrol; the diamine (8.5 g.) formed fine, grey-tinged needles, m. p. 271° (darkening above 256°), from ethanol, with amphoteric properties (Found : C, 69.7; H, 7.1; N, 10.8. Calc. for C<sub>15</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub> : C, 69.8; H, 7.0; N, 10.9%); Széki gave m. p. 218—219°.

2 : 2-Di-(2-methyl-5-benzoxazolyl)propane (IV; R = H).—A mixture of the foregoing diamine (1 g.) and acetic anhydride (5 g.) was refluxed for 3 hr., and the product vacuum-distilled; recrystallisation gave prisms (0.5 g.), m. p. 72°, from light petroleum (Found : C, 74.0; H, 5.9. C<sub>19</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub> requires C, 74.5; H, 5.9%).

2 : 2-Di-(4-hydroxy-3-methyl-5-nitrophenyl)propane.—A suspension of the condensation product (20 g.) of acetone with *o*-cresol in acetic acid, when treated with nitric acid (11 g.) in the usual way, gave a single *product*, crystallising as yellow needles (9 g.), m. p. 195°, from acetic acid (Found : C, 58.8; H, 5.2. C<sub>17</sub>H<sub>18</sub>O<sub>6</sub>N<sub>2</sub> requires C, 59.0; H, 5.2%).

2 : 2-Di-(2 : 4-dimethyl-5-benzoxazolyl)propane (IV; R = Me).—Reduction of the foregoing dinitro-compound (8.5 g.) with stannous chloride (40 g.) gave a diamine (5 g.) which was heated for 3 hr. with acetic anhydride; after vacuum-distillation, the *product* formed prisms, m. p. 127°, from methanol (Found : C, 75.3; H, 6.5. C<sub>21</sub>H<sub>22</sub>O<sub>2</sub>N<sub>2</sub> requires C, 75.4; H, 6.6%).

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