IX.—*Syntheses of Glucosides. Part VII. The Synthesis of 6-Bromoindican.*

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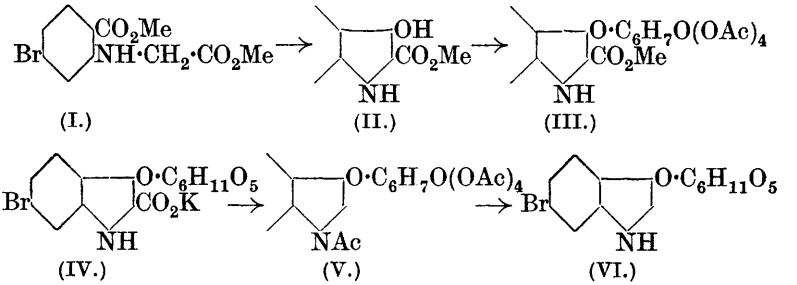
The general method devised by one of us (A. R.) for the preparation of 3-β-glucosidoxyindoles (J., 1927, 1937) has been applied to the synthesis of 6-*bromo*-3-β-*glucosidoxyindole* (6-*bromoindican*) (VI) according to the following scheme :



Methyl 4-*bromoanthranilate*, unlike methyl anthranilate, failed to react with methyl chloroacetate when the two substances were heated alone or in the presence of anhydrous sodium acetate (or pyridine). The *dimethyl* ester (I) was obtained by the esterification of 5-bromophenylglycine-2-carboxylic acid, which is formed in almost theoretical yield by the condensation of 4-bromoanthranilic and chloroacetic acids in warm alkali (Friedländer, Bruckner, and Deutsch, *Annalen*, 1912, **388**, 23. Heller and Hessel, *J. pr. Chem.*, 1928, **120**, 64, were unable to prepare the analogous chloro-acid by this method). The conversion of (I) into (II) by ring closure, which was effected by sodium in boiling benzene containing a trace of sodium methoxide, did not proceed so readily as the formation of methyl indoxylate from methyl phenylglycine-*o*-carboxylate (Robertson, *loc. cit.*). Heller and Hessel (*loc. cit.*) have noted that the analogous chloro-compound could not be converted into methyl 6-chloroindoxylate by heating with sodium methoxide solution.

6-Bromoindican closely resembles indican itself in properties and on hydrolysis under various conditions it gives analogous products. In the presence of an oxidising agent, *e.g.*, *p*-nitrosodimethylaniline, the liberated 6-bromoindoxyl is instantly oxidised with the formation of 6 : 6′-dibromoindigotin. The latter compound has been shown by Friedländer and his co-workers (*Ber.*, 1909, **42**, 765; 1922, **55**, 1655; *Annalen*, 1912, **388**, 23) to be the main constituent of " purple of the ancients " (Tyrian purple), which is formed by the

action of light on an unknown precursor present in the glands of certain marine molluscs.

Under appropriate conditions the 6-bromoindoxyl condenses with *p*-nitrobenzaldehyde and with isatin, yielding p-*nitrobenzaldehyde*-6-*bromoindogenide* and 6-*bromoindirubin* respectively.

Owing to the small amount of material available, attempts to prepare and isolate 6-bromoindoxyl from 6-*bromoindoxylic acid* were unsuccessful. Vigorous acetylation of the latter substance gave only a small yield of diacetyl-6-bromoindoxyl.

EXPERIMENTAL.

Methyl 4-*Bromoanthranilate*.—4-Bromoanthranilic acid was prepared by the method of Friedländer, Bruckner, and Deutsch (*loc. cit.*), the oxidation of 4-bromo-2-acetamidotoluene, however, being carried out at 105° instead of 80°.

The *methyl* ester was obtained by refluxing a mixture of the acid (20 g.), methyl alcohol (200 c.c.), and sulphuric acid (40 c.c.) for 8 hours. Part of the alcohol (100 c.c.) was removed by distillation, the residue poured into ice-water (200 c.c.), and the ester precipitated by excess of sodium carbonate. Crystallised from 50% methyl alcohol, it formed colourless needles (21 g.), m. p. 78° (Found : C, 41·9; H, 3·7; Br, 34·7. $C_8H_8O_2NBr$ requires C, 41·8; H, 3·5; Br, 34·8%).

Dimethyl 5-*Bromophenylglycine*-2-*carboxylate* (I).—A solution of 4-bromoanthranilic acid (21·6 g.) and chloroacetic acid (9·4 g.) in 5·5% aqueous potassium hydroxide (200 c.c.) was refluxed for several hours. Potassium 5-bromophenylglycine-2-carboxylate (22 g.), which crystallised on cooling (compare Friedländer, Bruckner, and Deutsch, *loc. cit.*), was heated (20 g.) with methyl alcohol (200 c.c.) and sulphuric acid (80 c.c.) under reflux for 3 hours. Addition of ice-water (800 c.c.), followed by excess of sodium carbonate, precipitated the *dimethyl* ester, which crystallised from methyl alcohol in tiny prisms (12 g.), m. p. 101° (Found : C, 43·7; H, 4·2. $C_{11}H_{12}O_4NBr$ requires C, 43·7; H, 4·0%).

Methyl 6-*Bromo*-3-*hydroxyindole*-2-*carboxylate* (II).—To pulverised sodium (2 g.) and dimethyl 5-bromophenylglycine-2-carboxylate (20 g.) in benzene (200 c.c.), methyl alcohol (0·1 c.c.) was added, and the mixture refluxed for 4 hours; the sodium derivative of *methyl* 6-*bromo*-3-*hydroxyindole*-2-*carboxylate* gradually separated. After cooling, the greenish-yellow solid was collected, washed with benzene, dried, and dissolved in water (800 c.c.). The solution was filtered after treatment with charcoal, and the ester precipitated by 50% acetic acid. Crystallised from dilute methyl alcohol and then from benzene, it formed colourless prisms (14 g.), m. p. 192° (Found : C, 44·2; H, 3·2. $C_{10}H_8O_3NBr$ requires C, 44·5; H, 3·0%). The

diacetyl derivative was obtained in almost theoretical yield when the ester (1 g.), fused sodium acetate (1 g.), and acetic anhydride (10 c.c.) were heated (oil-bath at 160°) for 2 hours; it crystallised from methyl alcohol in rhombic prisms, m. p. 151° (Found: C, 47·6; H, 3·6. $C_{14}H_{12}O_5NBr$ requires C, 47·5; H, 3·4%).

A solution of the ester (1 g.) in 5% methyl-alcoholic sodium hydroxide (20 c.c.) was refluxed for 1½ hours in an atmosphere of nitrogen. Next day, the colourless potassium salt was collected, washed with methyl alcohol, and dissolved in the minimum amount of water. Dilute hydrochloric acid precipitated 6-bromoindoxylic acid (0·7 g.), which separated from warm water as a *trihydrate* in aggregates of prisms, m. p. 198° (decomp.) (Found: C, 34·7; H, 3·5. $C_9H_6O_3NBr,3H_2O$ requires C, 34·8; H, 3·9%). Dried at 100°, the substance was dehydrated and then melted at 210°.

Acetylation of 6-bromoindoxylic acid (0·5 g.) by means of acetic anhydride (2 c.c.) and sodium acetate (0·5 g.) during 1 hour at 160° (oil-bath) gave 6-bromo-1-acetyl-3-acetoxyindole. Repeated crystallisation from dilute alcohol finally gave this substance as a *hydrate* in colourless prisms, m. p. 150—152° after sintering at 122° (Found: C, 45·8; H, 3·8. $C_{12}H_{10}O_3NBr,H_2O$ requires C, 45·7; H, 4·1%). Friedländer, Bruckner, and Deutsch (*loc. cit.*) record 118·5° as the melting point of this compound but do not give the analysis.

Methyl 6-*Bromo*-3-O-*tetra-acetyl*-β-*glucosidoxyindole*-2-*carboxylate* (III).—A cooled solution of potassium hydroxide (2 g.) in water (15 c.c.) was gradually added with stirring to a solution of methyl 6-bromoindoxyl-2-carboxylate (10 g.) and *O*-tetra-acetyl-α-glucosidyl bromide (15·2 g.) in acetone (100 c.c.) at 10°. When, after remaining at room temperature for 5 hours, the mixture was poured into ice-water (400 c.c.), the *tetra-acetyl glucoside* separated as a dark oil which solidified. The compound crystallised from methyl alcohol (charcoal) in clusters of colourless elongated prisms (14 g.), m. p. 171°, $[\alpha]_D^{20°}$ — 59·7° (in acetone) (Found: C, 48·2; H, 4·5; N, 2·3. $C_{24}H_{26}O_{12}NBr$ requires C, 48·0; H, 4·3; N, 2·3%). It is sparingly soluble in ether and readily soluble in acetone or warm alcohol. A penta-acetyl derivative could not be obtained.

6-*Bromo*-1-*acetyl*-3-O-*tetra-acetyl*-β-*glucosidoxyindole* (*Penta-acetyl*-6-*bromoindican*) (V).—Potassium hydroxide (5 g.), dissolved in methyl alcohol (30 c.c.), was gradually added to a suspension of the ester (III) (5 g.) in methyl alcohol (75 c.c.). After the solid had dissolved, the solution was heated on the steam-bath for 1 hour and *potassium* 6-*bromo*-3-β-*glucosidoxyindole*-2-*carboxylate* (IV) separated. Next day, the crystalline salt (3·5 g.) was collected, washed with methyl alcohol, and dried (Found: C, 39·3; H, 3·2; Br, 17·4. $C_{15}H_{15}O_8NBrK$ requires C, 39·5; H, 3·3; Br, 17·5%). A warm

aqueous solution of the substance gradually became pink. Liberated from the salt by means of cold dilute hydrochloric acid, the glucoside of 6-bromoindoxylic acid formed a gel which could not be crystallised. Prolonged hydrolysis of the glucoside by hot dilute hydrochloric acid in the presence of ferric chloride gave 6 : 6′-dibromoindigotin and glucose.

A mixture of the potassium salt (IV) (3 g.), fused sodium acetate (3 g.), and acetic anhydride (45 c.c.) was heated on the steam-bath for 1 hour and then at 160° (oil-bath) for 1 hour. On addition of ice-water to the cooled mixture, *penta-acetyl-6-bromoindican* (V) separated as an oil which crystallised in the course of 24 hours. Recrystallised from methyl alcohol (charcoal), it formed elongated prisms (3 g.), m. p. 159°, $[\alpha]_D^{20°}$ — 48·8° (in acetone) (Found : C, 49·5; H, 4·8; N, 2·3. $C_{24}H_{26}O_{11}NBr$ requires C, 49·3; H, 4·5; N, 2·4%). The compound is sparingly soluble in cold and readily soluble in hot alcohol, acetone, or chloroform.

6-*Bromo*-3-β-*glucosidoxyindole* (6-*Bromoindican*) (VI).—Dry methyl alcohol (120 c.c.) containing finely powdered penta-acetate (4 g.) in suspension was saturated at 0° with dry ammonia. The solid quickly dissolved and the solution was then kept at 0° for 17 hours. After removal of the ammonia and methyl alcohol in a vacuum, the residual oil was freed from acetamide by exposure to a high vacuum (1 mm. at 100°) for 1 hour. A solution of the amber-coloured residue in warm water was filtered after treatment with charcoal and, on cooling, 6-*bromo*-3-β-*glucosidoxyindole* (VI) separated as a tetrahydrate in silky leaflets, m. p. 64° after sintering at 52—54°, $[\alpha]_D^{20}$ — 6·4° (in acetone) (Found in air-dried specimen : C, 37·7; H, 5·5. $C_{14}H_{16}O_6NBr,4H_2O$ requires C, 37·7; H, 5·4%). When dried in a vacuum over phosphoric oxide for 60 hours, the compound lost part of its water of crystallisation; it then melted at 177° after sintering at 84° (Found : C, 44·1; H, 4·6. $C_{14}H_{16}O_6NBr,\frac{1}{2}H_2O$ requires C, 43·9; H, 4·5%). Further dehydration at 110° for 15 hours and finally at 160° for 5 minutes gave the anhydrous substance (Found : C, 45·0; H, 4·4. $C_{14}H_{16}O_6NBr$ requires C, 44·9; H, 4·3%).

6-Bromoindican is rapidly hydrolysed by warm 2% hydrochloric acid and by emulsin at 35—37° with the liberation of glucose and 6-bromoindoxyl, which is partly oxidised in the air to 6 : 6′-dibromoindigotin. If, however, ferric chloride is added and air is bubbled through the warm acid solution, the liberated bromoindoxyl is instantaneously oxidised to the pure indigotin. When a drop of concentrated hydrochloric acid is added to a solution of the glucoside in warm glacial acetic acid containing a little *p*-nitrosodimethylaniline as an oxidising agent, reddish-violet microscopic prisms of 6 : 6′-dibromoindigotin quickly separate.

Hydrolysis of the glucoside by warm 3% hydrochloric acid in the presence of isatin gave a quantitative yield of 6-*bromoindirubin*, which crystallised from hot aniline in purple prisms with a green metallic sheen. This compound does not melt below 340° (Found : C, 56·3; H, 2·8. $C_{16}H_{19}O_2N_2Br$ requires C, 56·3; H, 2·6%). When isatin is replaced by *p*-nitrobenzaldehyde, the latter condenses with 6-bromoindoxyl to give p-*nitrobenzaldehyde*-6-*bromoindogenide*, which separates from warm acetone in brick-red microscopic prisms, m. p. 297—298° (Found : C, 52·5; H, 2·6. $C_{15}H_9O_3N_2Br$ requires C, 52·2; H, 2·6%).

We are indebted to the Department of Scientific and Industrial Research for a maintenance grant which enabled one of us (R. B. W.) to take part in this investigation, and to the Chemical Society for grants which partly defrayed the cost of the materials. Our thanks are also due to Mr. L. W. Mullinger, B.Sc., who assisted us in the preparation of a quantity of 4-bromoanthranilic acid.

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University of London. [*Received, November 19th*, 1930.]