115. *Synthesis of Polyhydroxyanthraquinones Related to Asperthecin.*

By J. H. Birkinshaw and Rachel Gourlay.

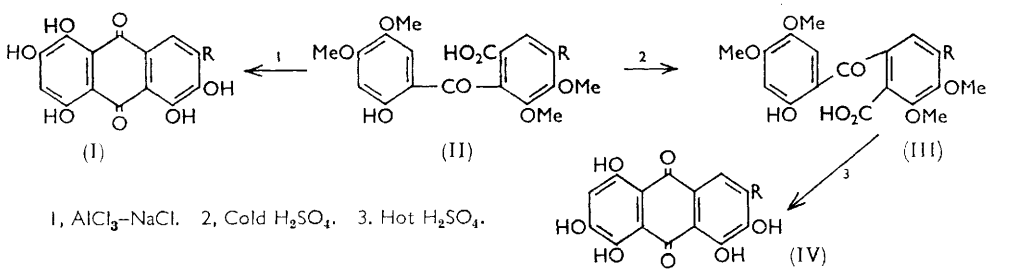
In presence of sulphuric acid 2-(2-hydroxy-4,5-dimethoxybenzoyl)-3,4-dimethoxybenzoic acid undergoes the Hayashi rearrangement, yielding 6-(2-hydroxy-4,5-dimethoxybenzoyl)-2,3-dimethoxybenzoic acid. The latter, on ring closure and demethylation, gives 1,3,4,5,6-pentahydroxyanthraquinone, the structure of which was confirmed by synthesis from 1,2,4-trimethoxybenzene and opianic acid.

Asperthecin, $C_{15}H_{10}O_8$, a metabolite of *Aspergillus quadrilineatus* Raper and Thom, was shown by Neelakantan, Pocker, and Raistrick [1] to be 2,3,4,5,6- or 1,2,4,5,6-pentahydroxy-7-hydroxymethylanthraquinone. Birkinshaw and Gourlay [2] proved the latter structure (I; R = CH_2·OH) by conversion of asperthecin into asperthecic acid (I; R = CO_2H) and decarboxylation of the acid into the pentahydroxyanthraquinone (I; R = H) which was identical with synthetic 1,2,4,5,6-pentahydroxyanthraquinone. The synthesis was achieved by condensing hemipinic anhydride in presence of aluminium chloride with 1,2,4-trimethoxybenzene to give 2-(2-hydroxy-4,5-dimethoxybenzoyl)-3,4-dimethoxybenzoic acid (II; R = H), monodemethylation having occurred. Ring closure of the benzoylbenzoic acid, when effected in a fused mixture of sodium and aluminium chloride, gave 1,2,4,5,6-pentahydroxyanthraquinone (I; R = H).

We now describe an earlier attempt to induce ring closure of the substituted benzoylbenzoic acid (II; R = H) in presence of hot concentrated sulphuric acid. This gave a different pentahydroxyanthraquinone which was at first thought to be the required substance. Further investigation showed that, in cold sulphuric acid, the acid (II; R = H), m. p. 225°, undergoes the Hayashi [3] rearrangement to an isomer, m. p. 171—172°, which

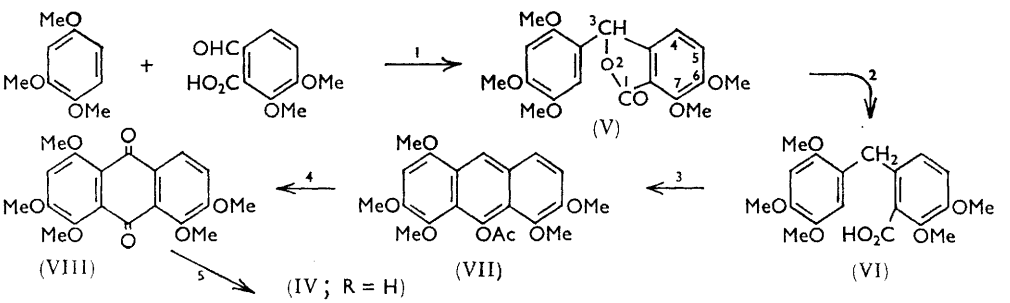
[1] Neelakantan, Pocker, and Raistrick, *Biochem. J.*, 1957, **66**, 234.
[2] Birkinshaw and Gourlay, *Biochem. J.*, 1961, **81**, 618.
[3] Hayashi, *J.*, 1927, 2516.

must be 6-(2-hydroxy-4,5-dimethoxybenzoyl)-2,3-dimethoxybenzoic acid (III; R = H). On ring closure the product obtained is 1,3,4,5,6-pentahydroxyanthraquinone (IV; R = H). The same pentahydroxyanthraquinone (IV; R = H) was obtained by heating 2-(2,5-dihydroxy-4-methoxybenzoyl)-3,4-dimethoxybenzoic acid [2] with sulphuric acid.



The structure of the product (IV; R = H) was confirmed by an unambiguous synthesis in relatively mild conditions, as illustrated in the chart. Opianic acid and 1,2,4-trimethoxybenzene in sulphuric acid form the lactone (V) which was reduced with zinc in alkaline solution to the acid (VI). Ring closure at 90° in a mixture of acetic acid and its anhydride containing zinc chloride then afforded the anthryl acetate (VII). The acetyl group was removed by methanolic potassium hydroxide in the cold, the product being spontaneously oxidised in air to the pentamethoxyanthraquinone (VIII). The final demethylation to the pentahydroxyanthraquinone (IV; R = H) was accomplished with hydrobromic acid. The product and its penta-acetate were identical with the materials obtained by the Hayashi rearrangement.

In a synthesis parallel with that of the anthraquinone (IV; R = H) the 7-methyl homologue (IV; R = Me) was prepared, starting with 5-methylhemipinic anhydride [1] in place of hemipinic anhydride. This was condensed (*a*) with 3-methoxyphenol to yield 2-(2-hydroxy-4-methoxybenzoyl)-3,4-dimethoxy-5-methylbenzoic acid, which then, by the



Elbs persulphate reaction,[2] afforded 2-(2,5-dihydroxy-4-methoxybenzoyl)-3,4-dimethoxy-5-methylbenzoic acid, or (*b*) with 1,3,4-trimethoxybenzene to yield 2-(2-hydroxy-4,5-dimethoxybenzoyl)-3,4-dimethoxy-5-methylbenzoic acid (II; R = Me). These two benzoylbenzoic acids, when heated with concentrated sulphuric acid, gave the same 1,3,4,5,6-pentahydroxy-7-methylanthraquinone (IV; R = Me), shown by the similarity of the ultraviolet spectra to have the same arrangement of hydroxyl groups as the lower homologue (IV; R = H). Thus the Hayashi rearrangement has again operated in this condensation.

The 7-methyl group of the product (IV; R = Me) was then converted into a hydroxymethyl group to obtain the product (IV; R = CH_2OH), an isomer and close relative of

asperthecin. It differed from asperthecin only in the transference of a hydroxyl group from the 2- to the 3-position, a divergence which was clearly reflected in the ultraviolet spectrum.

Experimental

Hayashi Rearrangement (II) ⟶ (III) (R = H).—2-(2-Hydroxy-4,5-dimethoxybenzoyl)-3,4-dimethoxybenzoic acid [2] (m. p. 225°; 0·4 g.) was dissolved in concentrated sulphuric acid (40 ml.) and kept for 4 hr. at 20°. The deep red solution was then poured into water, and the mixture was heated to 100°, the colour of the solution and precipitate fading. After chilling, the crystals were collected and recrystallized from ethanol, giving pale yellow needles of 6-(2-*hydroxy*-4,5-*dimethoxybenzoyl*)-2,3-*dimethoxybenzoic acid* (III; R = H), m. p. 171—172° (Found, on sample dried immediately before analysis: C, 59·5; H, 5·0; OMe, 34·4. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0; 4OMe, 34·2%).

1,3,4,5,6-*Pentahydroxyanthraquinone* (IV; R = H).—2-(2-Hydroxy-4,5-dimethoxybenzoyl)-3,4-dimethoxybenzoic acid (II; R = H; 0·70 g.) was heated with concentrated sulphuric acid (15 ml.), the bath-temperature being held for 15 min. at 145—150°, 20 min. at 150—155°, and 40 min. at 155—160°. The colour of the solution changed from intense red to violet. When cool, the mixture was poured into cold water (200 ml.), the temperature of which was raised to 100° to coagulate the dark brown precipitate. This was then collected, washed, and dried. The crude product was heated with acetic anhydride (10 ml.) containing concentrated sulphuric acid (0·2 ml.) at 100° for 5 min. The solution was cooled and poured into water; the precipitate (0·58 g.) was collected and thrice crystallized from methanol, which afforded pale yellow needles of 1,3,4,5,6-*penta-acetoxyanthraquinone*, m. p. 240—241° (Found: on product dried at 100° in a high vacuum: C, 57·9; H, 3·8; Ac, 45·6. $C_{24}H_{18}O_{12}$ requires C, 57·8; H, 3·6; 5Ac, 43·1%).

The penta-acetate (0·10 g.) was refluxed with methanol (10 ml.) containing concentrated sulphuric acid (0·3 ml.) for 90 min. The dark red needles, m. p. 303—305° (decomp.), deposited on cooling consisted of 1,3,4,5,6-*pentahydroxyanthraquinone* (IV; R = H), $\lambda_{max.}$ (in EtOH) 240, 263, 283, 311, 501, 526 mμ (log ε 4·36, 4·38, 4·11, 4·10, 4·11, 4·04, respectively) (Found, on product dried at 100° *in vacuo*: C, 58·3; H, 3·0. $C_{14}H_8O_7$ requires C, 58·3; H, 2·8%). The product gives an intense violet colour with concentrated sulphuric acid and in acetic acid shows no fluorescence in daylight.

6,7-*Dimethoxy*-3-(2,4,5-*trimethoxyphenyl*)*phthalide* (V).—Opianic aid (8·76 g.) and 1,2,4-trimethoxybenzene (7 g.) were mixed and chilled; 73% sulphuric acid (H_2SO_4 : H_2O = 40 : 27 v/v; 22 ml.) was added with stirring. Some heat was evolved and the solid dissolved. After about 90 min. the red mixture had become paler and deposited crystals. It was treated with water and the product was collected, washed and crystallized from aqueous acetic acid to yield the hydrated *phthalide* (14·5 g.), m. p. 109—110° (Found: OMe, 37·8. $C_{19}H_{20}O_7,3H_2O$ requires 3OMe, 37·45. Found, after drying at 80° *in vacuo*: C, 63·6; H, 5·3. $C_{19}H_{20}O_7$ requires C, 63·3, H, 5·6%).

2,3-*Dimethoxy*-6-(2,4,5-*trimethoxybenzyl*)*benzoic acid* (VI).—The hydrated phthalide (12·4 g.) was boiled under reflux with zinc powder (20 g.) and 2N-sodium hydroxide (150 ml.). Further additions of zinc (10 g.) and alkali (75 ml.) were made on three occasions during the heating (20 hr.). The solution was filtered, acidified with concentrated hydrochloric acid, and warmed to lactonize any unchanged material. After cooling, the aqueous phase was poured off and the gummy residue was treated with 2N-sodium carbonate in which most of it dissolved. The residual phthalide (1·75 g.) was removed by filtration. The gum precipitated on acidification of the filtrate solidified and recrystallized from aqueous acetic acid as a hydrate, forming rods, m. p. 84—89° (10·2 g.). Recrystallization from ether–light petroleum afforded anhydrous 2,3-*dimethoxy*-6-(2,4,5-*trimethoxybenzyl*)*benzoic acid*, m. p. 135° (Found: C, 62·85; H, 6·25; OMe, 42·7. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·1; 5 OMe, 42·8%).

1,3,4,5,6-*Pentamethoxy*-10-*anthryl Acetate* (VII).—The benzylbenzoic acid (5 g.), acetic anhydride (20 ml.), acetic acid (35 ml.), and zinc chloride (0·5 g.) were warmed at 90° for 1 hr. An intense green fluorescence rapidly developed. The mixture was poured into water, forming a gum. The aqueous portion was decanted and the gum was rubbed with ether. The yellow powder so obtained was collected and washed with a little methanol. Lemon-yellow needles, m. p. 145° (1·7 g.), of the *anthryl acetate* were thus obtained (Found: C, 65·3; H, 5·8; OMe,

40·1. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7; 5OMe, 40·15%). The ether mother-liquor contained some unchanged starting material.

1,3,4,5,6-*Pentamethoxyanthraquinone*.—The anthryl acetate (3·88 g.) was dissolved at 55° in methanol (400 ml.) containing potassium hydroxide (20 g.) and was left exposed to the air at 24° for 3 days; the fluorescence disappeared. The solution was acidified to Congo Red with concentrated hydrochloric acid (26 ml.), chilled, and filtered. The residue obtained on removal of methanol was extracted with ether (~500 ml.). The ether solution was dried (Na_2SO_4) and concentrated, yielding yellow prisms (1·63 g.) of 1,3,4,5,6-*pentamethoxyanthraquinone*, m. p. 162° (Found: C, 63·6; H, 5·1; OMe, 43·7, 43·2. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1; 5 OMe, 43·3%).

1,3,4,5,6-*Pentahydroxyanthraquinone*.—1,3,4,5,6-Pentamethoxyanthraquinone (54 mg.) was heated in a sealed tube with a 50% w/v solution (3 ml.) of hydrogen bromide in acetic acid at 150—170° for 2 hr. The mixture was poured into water. The brown amorphous precipitate was collected and purified by acetylation and crystallization of the acetyl derivative. Yellow needles (14·5 mg.) of the penta-acetate were obtained of m. p. 238—240°, unchanged on admixture with a specimen of the penta-acetate obtained by means of the Hayashi rearrangement. The product (10·8 mg.) was hydrolysed to the 1,3,4,5,6-pentahydroxyanthraquinone. The m. p., 302—306° (decomp.) after recrystallization, was not depressed on admixture with the pentahydroxyanthraquinone obtained by the Hayashi rearrangement. The two products also agreed in ultraviolet absorption spectrum.

1,3,4,5,6-*Pentahydroxy-7-methylanthraquinone* (IV: R = Me). The synthesis of this product, starting from 5-methylhemipinic anhydride, instead of hemipinic anhydride, by condensation with (*a*) *m*-methoxyphenol or (*b*) 1,2,4-trimethoxybenzene, followed the methods used for the lower homologue, and is not described in detail. The products were:

2-(2-*Hydroxy*-4-*methoxybenzoyl*)-3,4-*dimethoxy*-5-*methylbenzoic acid*, prisms, m. p. 207—208° (Found: C, 62·5; H, 5·1; OMe, 27·3. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2; 3OMe, 26·9%).

2-(2,5-*Dihydroxy*-4-*methoxybenzoyl*)-3,4-*dimethoxy*-5-*methylbenzoic acid*, pale yellow plates m. p. 228—230° (decomp.), giving a strong blue-green ferric colour in ethanol, lightening on addition of water, and an intense red in sulphuric acid, becoming bluish-purple on heating (Found, on material dried at 100° in a high vacuum: C, 58·3; H, 5·3; OMe, 25·8. $C_{18}H_{18}O_8,0{\cdot}5H_2O$ requires C, 58·2; H, 5·2; 3OMe 25·1%) [the water retained at 100° was not completely lost even at 120° (Found: C, 59·1; H, 5·4. Calc. for $C_{18}H_{18}O_8$: C, 59·7; H, 5·0%)].

1,3,4,5,6-*Penta-acetoxy*-7-*methylanthraquinone*, cream-coloured needles, m. p. 241—242° (decomp.) (Found: C, 58·15; H, 3·95. $C_{25}H_{20}O_{12}$ requires C, 58·6; H, 3·9%).

1,3,4,5,6-*Pentahydroxy*-7-*methylanthraquinone*, deep red crystals with bronzy lustre (from methanol), m. p. 308—310° (decomp.), giving a violet colour with sulphuric acid, not fluorescing in acetic acid in daylight (Found, on sublimed sample: C, 59·3; H, 3·4. $C_{15}H_{10}O_7$ requires C, 59·6; H, 3·3%), $\lambda_{max.}$ (in EtOH) 238, 268, 285, 313, 416 (infl.), 499, 527 (log ε 4·38, 4·47, 4·24, 4·17, 3·69, 4·12, 4·08, respectively).

2-(2-*Hydroxy*-4,5-*dimethoxybenzoyl*)-2,3-*dimethoxy*-4-*methylbenzoic acid*, faintly yellow prisms, m. p. 190° (Found: C, 60·9; H, 5·4; OMe, 32·8. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·4; 4OMe, 33·0%)

1,3,4,5,6-Pentahydroxy-7-methylanthraquinone and its penta-acetate prepared by method (*b*) were identical with the corresponding products prepared by method (*a*).

1,3,4,5,6-*Pentahydroxy*-7-*hydroxymethylanthraquinone*—1,3,4,5,6-Penta-acetoxy-7-methylanthraquinone (0·60 g.) was refluxed with *N*-bromosuccinimide (0·40 g.) and benzoyl peroxide (0·07 g.) in dry carbon tetrachloride (200 ml.) for 50 hr. Only a part of the material dissolved. The undissolved matter was separated and again subjected to the reaction with fresh reagents. After three repetitions of the process, practically all the penta-acetate had reacted. The crystals obtained on evaporation to dryness were collected, washed with hot water to remove unchanged bromosuccinimide, and recrystallized from ethyl acetate. Yellow crystals (0·29 g.) of the bromo-derivative were obtained. This product was refluxed with acetic anhydride (6·0 ml.) and anhydrous sodium acetate (0·6 g.) for 75 min., cooled, and poured into water, and the dark product (0·26 g.) was collected. Recrystallization from methanol afforded a pale yellow crystalline *acetate* (0·12 g.), m. p. 242—244°. This was hydrolysed by refluxing methanol (10 ml.) containing sulphuric acid (0·3 ml.) for 90 min. The product recovered by pouring the mixture into water recrystallized from methanol, affording 1,3,4,5,6-*pentahydroxy*-7-*hydroxymethylanthraquinone*, red acute-angled plates and needles, not melting up to 275°, $\lambda_{max.}$ (in

EtOH) 241, 266, 287, 312, 410—415 (infl.), 501, 525—530 (infl.) (log ε 4·36, 4·41, 4·21, 4·17, 3·63, 4·13, 4·03, respectively) (Found, on material dried at 100° *in vacuo*: C, 56·8, H, 2·85. $C_{15}H_{10}O_8$ requires C, 56·6; H, 3·2%).

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Department of Biochemistry, London School of Hygiene and Tropical Medicine,
(University of London),
Keppel Street, London, W.C.1. [*Received, August* 30*th*, 1962.]