Synthesis of Compounds Related to Muscarufin I

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The synthesis and properties of 2,5-dimethoxy-1,4-bis-(2-carboxymethoxyphenyl)-benzene (II), 2,5-bis-(2-carbomethoxyphenyl)-benzoquinone (III) and some related compounds is reported. These compounds embrace parts of the structure proposed by Kögl and Erxleben for muscarufin (I).

From the common fly-agaric, Amanita muscaria, Kögl and Erxleben\(^1\) isolated in 1930 a red pigment muscarufin for which, as a result of elegant degradative work carried out with very small quantities of material, they were able to advance structure I. This formula appears to have met with general acceptance.

Other products of fungal metabolism which exhibit structural relationships to muscarufine include polyporic acid\(^2\), atramentin\(^3\) and leucomelone\(^4\) which all possess the terphenyl system in common with muscarufin. The unsaturated side chain of muscarufin recurs in the widespread fungus and lichen pigment teleporic acid\(^5\) and is somewhat reminiscent of polyenoid pigments of fungal origin, e.g. corticrin\(^6\), cortisalin\(^7\), fumigallin\(^8\) and limococrin\(^9\). Among natural products from higher plants compounds of the piperic acid type are worthy of mention.

Some of these compounds have been synthesised and the bis-phenyl-dihydroxybenzoquinones in particular have been the subject of a number of investigations.

Since the work of Kögl and Erxleben, however, no further publications on muscarufin have appeared and a synthetic confirmation of the proposed structure is still lacking.

In order to obtain information about the synthetic pathways to, and the properties of, 2,5-bis-(2-carboxyphenyl)-benzoquinone and related compounds the present investigation was undertaken.

In view of the successful application of the Ullmann reaction for the preparation of tri- and tetraquinone\(^{10}\) we have explored this approach for the synthesis of muscarufin-like substances.

The mixed Ullmann coupling of methyl 2-bromobenzoate and 2,5-diiodohydroquinone dimethylether afforded 2,5-dimethoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene (II) in good yield (50\%\,). On treatment with nitric acid it furnished the yellow 2,5-bis-(2-carbomethoxyphenyl)-benzoquinone (III).
We have investigated the possibilities of introducing various substituents into the central nucleus of these terphenyl systems. All attempts to brominate the terphenyl derivative II failed and the reaction between the quinone III and hydrogen bromide afforded the dilactone IV ($R=H$); the hydrogen bromide thus simply reduced the quinone. The same dilactone resulted from demethylation of II with pyridinium chloride and was even obtained on attempted reductive acetylation of the quinone. This fact is of interest since Kögl and Erxleben report that muscarufin under similar conditions did not undergo lactonisation but yielded a *triacetate*. The addition of hydrogen chloride to III was more successful but lactonisation again occurred with formation of the chlorodilactone (IV, $R=Cl$). These lactones are very high melting, sparingly soluble substances and it is therefore sometimes difficult to isolate them in a state of complete purity. They can be dissolved in hot, strong alkali but on acidification the dilactones are recovered. Repeated treatment of the dilactone IV ($R=H$) with potassium hydroxide and methyl iodide afforded the monolactone methyl ether methyl ester (V).

Thiele acetylation of the quinone III using sulphuric acid as a catalyst failed. However, when perchloric acid was employed a complex reaction product was obtained, from which 2,3,5-triacetoxy-1,4-bis-(2-carbomethoxyphenyl)-benzene (VI) could be isolated although in poor yield. This compound contains all the characteristic features of *leuco*-muscarufin except the unsaturated side chain.

Further work on this subject is in progress and will be published shortly in this journal.

MUSCARUFIN-LIKE COMPOUNDS I

EXPERIMENTAL

All melting points are uncorrected. Melting points above 300° were determined by dropping a few crystals on a preheated block; the very strong sublimation of the substances in question prohibited the use of ordinary methods.

2,5-Dimethoxy-1,4-bis-(2-carboxymethylphosphonyl)-benzene (II). 2,5-Diiodohydroquinone dimethylether (25 g, 0.1 mole) and methyl 2-bromobenzoate (84 g, 0.4 mole) were heated in a 300 ml flask until a homogeneous solution was obtained. This was thoroughly mixed with copper bronze (240 g) and then slowly heated in a salt bath. At ca. 200° a considerable heat of reaction developed and the temperature rose to ca. 300°. After cooling to room temperature the hard mass was disintegrated and exhaustively extracted with chloroform in a Soxhlet apparatus. The solvent was removed and the residual oil (A) distilled in vacuo yielding a small amount of methyl benzoate, dimethyl diphenate and an oily fraction b.p. 200–285° (1 mm) the bulk of which passed over at about 240°. On trituration with methanol the fraction b.p. 200–285° crystallised (12 g, 48%). Alternatively methanol (50 ml) was added to the crude oil (A) and after keeping in the refrigerator overnight most of the terphenyl derivative crystallised leaving the dimethyl diphenate in the mother liquors. Recrystallisation from glacial acetic acid gave the pure compound as small colourless prisms, m. p. 174–175°. (Found: C 70.9; H 5.5; CH₃O 30.9. Calc. for C₁₄H₁₄O₄: C 70.9; H 5.5; CH₃O 30.5.)

2,5-Bis-(2-carboxymethylphosphonyl)-benzoquinone (III). 2,5-Dimethoxy-1,4-bis-(2-carboxyphosphonyl)-benzene (10 g) was slowly added to nitric acid (150 ml, d 1.42). The initial dark coloration rapidly disappeared and nitrous fumes were evolved. The suspension was allowed to stand for 15 minutes and was then poured into water (500 ml). After standing overnight the yellow precipitate was collected and recrystallised from methyl-ethyl ketone giving the pure quinone as yellow prisms, m. p. 188–189°. (Found: C 70.0; H 4.4; CH₃O 16.2. Calc. for C₁₆H₁₄O₄: C 70.2; H 4.3; CH₃O 16.5.)

2,5-Dihydroxy-1,4-bis-(2-carboxymethylphosphonyl)-benzene dilactone (IV, R = H). (a). The quinone III (0.20 g) was dissolved in chloroform (20 ml) and a rapid stream of hydrogen bromide passed into the solution. After an initial dark coloration white crystals began to separate. When the precipitation appeared complete the crystals were collected (0.19 g) and recrystallised from dicetone alcohol giving needles, m. p. ca. 410°, subliming readily above 300°. Qualitative tests showed the absence of bromine.

(b). Attempted reductive acetylation of III using acetic anhydride, zinc dust and a trace of pyridine or fused sodium acetate led to the formation of a white flocculent precipitate, which was separated from excess zinc by decantation. Recrystallisation from very large volumes of acetic anhydride afforded small white needles, m. p. ca. 410°, alone or in admixture with the substance obtained in experiment (a). Determination of the acetyl content (about 2%) indicated the almost complete absence of acetoxyl groups.

(c). Treatment of the terphenyl derivative II with excess pyridinium chloride at 200° for 2 h resulted in the formation of the same dilactone as in experiments (a) and (b) as shown by melting point and mixed melting point determinations. (Found: C 75.9; H 3.2. Calc. for C₁₆H₁₄O₄Cl: C 75.4; H 3.2.)

2,5-Dihydroxy-3-chloro-1,4-bis-(2-carboxymethylphosphonyl)-benzene dilactone (IV, R = Cl). The quinone III (0.25 g) was dissolved in chloroform and a stream of hydrogen chloride passed into the solution. The product soon separated as white crystals (0.16 g), which were recrystallised from dicetone alcohol (needles), m. p. ca. 385°. (Found: C 68.3; H 2.6; Cl 10.7. Calc. for C₁₆H₁₄O₄Cl: C 68.9; H 2.6; Cl 10.2.)

2-Hydroxy-5-methoxy-1-(2-carboxyphosphonyl)-4-(2-carboxymethylphosphonyl)-benzene lactone (V). The dilactone IV (R = H) (0.9 g), potassium hydroxide (0.9 g) and methanol (10 ml) were heated on a water bath until a clear solution was obtained (0.5 h). Methyl iodide (4.3 g) was added and the mixture refluxed for 6 h. Additional quantities of potassium hydroxide (0.1 g) and methyl iodide (1 g) were introduced and the heating continued for a further 6 h. The solvent was removed and the solid residue (A) extracted several times with boiling chloroform. The extract was evaporated to dryness and the product (0.4 g) recrystallised from methanol (small needles), m. p. 197–198°. (Found: C 73.5; H 4.6. Calc. for C₁₇H₁₅O₄: C 73.3; H 4.5.) From the chloroform insoluble part of A unchanged starting material was recovered.

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2,3,5-Triacetoxy-1,4-bis-(2-carboxethoxyphenyl)-benzene (VI). Perchloric acid (15 ml, \(d\) 1.07) was slowly added to acetic anhydride (300 ml), cooled in an ice bath. The temperature of the solution was then allowed to rise to ca. 20° and the quinone III (7.4 g) introduced with stirring. After about 5 h it had dissolved giving a brownish red solution, which was kept overnight and then poured onto ice (1 kg). Water (2 l) was added and the suspension stirred for 24 h. The dried precipitate (A) (8.5 g) was dissolved in benzene (a small amount of insoluble amorphous material being removed by filtration), and the solution evaporated to a small volume. On standing some crystalline material was deposited (B), which was, however, found to be a difficulty resolvable mixture. (M. p. of the components ca. 160° and ca. 180°.) The mother liquor was rapidly (compare below) passed through a column of activated alumina (15 × 2 cm), which was then thoroughly washed with benzene. Evaporation of the purified solution yielded an oil, which on treatment with benzene afforded unchanged starting material. Addition of ligroin to the mother liquor precipitated a yellowish mixture of crystals yielding on fractional crystallisation from methanol and benzene-ligroin mixtures small amounts of starting material, a mixture of higher melting compounds (B) and the desired product (ca. 2 g). The last named formed colourless prisms finally purified by recrystallisation from methyl cyclohexane, m. p. 144 — 145°. (Found: C 64.1; H 4.5. Calc. for C\(_{21}\)H\(_{14}\)O\(_{12}\): C 64.6; H 4.6.)

If the reaction was carried out at a slightly elevated temperature (30°) or for a prolonged time the amount of starting material recovered decreased, the amount of triacetate remained approximately constant but that of the higher melting unidentified compounds (B) increased.

In preliminary experiments the crude reaction product (A) was treated with dimethyl sulphate and alkali giving, in poor yield, a compound which according to its properties and the analytical result was a diacetoacitie of 2,3,5-trihydroxy-1,4-bis-(2-carboxyphenyl)-benzene methyl ether (e. g. IV, R = OCH\(_3\)). On recrystallisation from acetic anhydride the diacetate was obtained as needles, m. p. ca. 310°. (Found: C 73.2; H 3.3; CH\(_2\)O 9.8. Calc. for C\(_{21}\)H\(_{14}\)O\(_4\): C 73.4; H 3.5; CH\(_2\)O 9.0.) In another experiment A was subjected to acetic acid methanalysis affording again in poor yield a compound, m. p. ca. 355°, after recrystallisation (needles) from acetic acid. This substance apparently was a diacetate of 2,3,5-trihydroxy-1,4-bis-(2-carboxyphenyl)-benzene, e. g. IV, R = OH). (Found: C 72.9; H 3.2. Calc. for C\(_{21}\)H\(_{14}\)O\(_4\): C 72.7; H 3.1.) Attempts were also made to separate the components of A by chromatography on activated alumina but on prolonged contact with the alumina the triacetate was apparently hydrolysed and the product strongly adsorbed.

REFERENCES

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