ACTA CHEMICA SCANDINAVICA 9 (1955) 210--215

Studies on Antimetabolites

VII *. Note on some Reaction Products Formed in the Oxidation of 4,6-Di-(α,α-dimethylbenzyl)pyrogallol with Alkaline Potassium Permanganate

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As reported earlier the oxidation of 4,6-di-(α,α-dimethylbenzyl)-pyrogallol with alkaline potassium permanganate yielded α-oxo-β-phenyl*iso*valeric acid as the main product. In addition there were isolated some α-phenyl*iso*butyric acid and two further acid products. These have now been subjected to a more detailed study and the structures II and III are proposed.

In Part I of this series it was reported that the oxidation of 4,6-di-*tert*alkyl substituted pyrogallols with alkaline potassium permanganate in aqueous solution afforded fairly good yields of the corresponding tri-substituted pyruvic acids as well as some of the α-phenyl*iso*butyric acid derivatives. The oxidation of 4,6-di-(α,α-dimethylbenzyl)pyrogallol (I) was studied in some detail and in addition to the ketoacid and α-phenyl*iso*butyric acid two further acid products, here termed A and B, were isolated from the reaction mixture. It is the purpose of the present communication to describe some reactions carried out with these products, and to propose probable structures.

Compound A melts at 174—175° and has the composition $C_{23}H_{24}O_3$. It does not dissolve in aqueous sodium bicarbonate solution and thus contains no carboxyl group, but dissolves readily in *N* sodium hydroxide. With ferric chloride an intense red colouration is obtained indicating the presence of enolic hydroxyl groups. Dimethyl sulphate and alkali converts the compound into a neutral mono-methyl ether, which does not give this colour reaction. From this evidence and the close analogy of the substance with a compound obtained by Campbell by aerial oxidation of 4,6-di-*tert*butylpyrogallol in alkaline solution for which he, as a result of thorough studies [2,3], suggests structure (IV) compound A is probably an enol of 3,5-di-(α,α-dimethylbenzyl)*cyclo*pentatrione-1,2,4.

Compound B, $C_{23}H_{26}O_6$, melts at 185—186° (decomp.) and is readily soluble in sodium bicarbonate solution. It gives a mono-*cyclo*hexylammonium salt and

* Part VI. *Acta Chem. Scand.* **9** (1955) 203.

a mono-piperidiniumsalt with excess of the basic reagents. With an excess of diazomethane it forms a mono-methyl derivative, $C_{23}H_{25}O_5(OCH_3)$, from which compound B is recovered after alkaline hydrolysis. Hence compound B obviously contains one free carboxyl group but no phenolic hydroxyl group. The presence of a free carboxyl is also demonstrated by titration with 0.1 *N* sodium hydroxide using phenolphthalein as indicator. One mole of alkali is consumed and the end-point of the titration is sharp. When compound B is boiled with 6 *N* sodium hydroxide, however, a solid di-sodium salt, $Na_2C_{23}H_{26}O_7$, separates. An aqueous solution of this salt has a strongly alkaline reaction, and compound B is recovered when the solution is made slightly acid, even in the cold. This behaviour indicates, that compound B, in addition to the free carboxyl group, contains a lactone group. A lactone (or ester) group is also suggested by the fact, that B gives a positive hydroxamate test.

All attempts to detect carbonyl functions in compound B by treatment with 2,4-dinitrophenylhydrazine or hydroxylamine were unsuccessful. Neither B nor its methyl ester gave any colouration with ferric chloride. Obviously they do not contain any enolisable carbonyl groups, and probably no other carbonyl groups. (Compound A, however, likewise failed to react with phenylhydrazine or hydroxylamine.)

When heated slightly above its melting point compound B readily loses one mole of water and is converted into an anhydrocompound, $C_{23}H_{24}O_5$, m.p. 187°. When dissolved in ethanol and treated with dilute sodium hydroxide this substance slowly consumes one mole of alkali and on acidification of the solution compound B is precipitated. The anhydrocompound is obviously the di-lactone corresponding to the mono-lactoneacid B. The presence of a free hydroxyl group in the anhydrocompound was shown by a Zerewitinoff determination, which indicated one "active" hydrogen atom.

Extensive oxidation of compound B with potassium permanganate in hot, strongly alkaline solution affords α-phenyl*iso*butyric acid. This proves, that the structural unit $C_6H_5—C(CH_3)_2—C$ is still present in compound B and the yield (58 % of theory) proves that there are two such groupings in the molecule.

From the evidence produced there seems to be little doubt, that compound B possesses structure III. The anhydrocompound must then be the dilactone V. The relation between compound B and the anhydrocompound V is also demonstrated by the formation from both the anhydrocompound and the methyl ester of compound B of the same reduction product, $C_{23}H_{32}O_5$, with lithium-aluminium hydride, the structure of which must be VI. The proposed structures are further supported by the infrared absorption spectrum of the anhydrocompound which in addition to the benzene bands shows strong bands at 2.82, 5.56 and 7.27 μ indicating the presence of respectively hydroxyl groups, α-lactone rings and methyl groups. There are no other bands in the 2.5 to 8 μ region.

Studies of molecular models allow certain conclusions to be drawn regarding the stereochemistry of the compounds. If in Formula III the lactone ring is considered to be oriented in the plane of the paper then the hydroxyl group on carbon atom 1 and the carboxyl on 3 must be on the same side of this plane in order to allow the ring closure to compound V. The two R-groups must both be on the opposite side to the above hydroxyl and carboxyl groups.

Nothing can be said about the orientation of the hydroxyl group attached to carbon atom 2. Theoretically two pairs of racemates may be formed when compounds V and VII are reconverted to III. The compound actually obtained, however, is homogeneous, which proves that the ring closure occurs with selective formation of one of these D,L-forms. In compounds V, VI and VII carbon atom 2 is not asymmetric, hence this uncertainty disappears, and these compounds are therefore derivatives of D,L-arabitol.

The behaviour of compound B and the pentol towards periodic acid in aqueous and dilute acetic acid solution was contradictory to the above arguments in favour of the proposed structures. The compounds were very slowly attacked and even after several days at room temperature the periodate consumption was only a fraction of that calculated. These results are surprising in view of the fact, that the diol (VIII), prepared by reduction of ethyl α-oxo-β-phenyl*iso*valerate with lithium-aluminium hydride, was rapidly and quantitatively split with the consumption of one mole of periodate. Studies on molecular models of compound B and the pentol show, however, that the bulky α-phenyl*iso*propyl groups leave very little space for the formation of an addition complex with the rather large periodate ion. The slow oxidation may thus be due to "steric hindrance". It is well-known, that the reaction velocity of the periodate oxidation of glycols is highly influenced by bulky neighbouring substituents (see *e.g.* Ref.[4]).

The low yield of the crystalline products II and III compared with the oily mixtures obtained on evaporation of the mother liquors suggests that further acid products (*e.g.* isomers of III) may have been formed in the oxidation of the pyrogallol derivative. This assumption is supported by the material balance. The yields of the various products obtained from 300 g of the pyrogallol derivative were:

Ethyl-α-oxo-β-phenyl*iso*valerate	118 g =	33 %
α-Phenyl*iso*butyric acid	24	9
Compound II	21	7
Compound III	15	4.5
		53.5 %

(The yields have been calculated as C_6H_5—$C(CH_3)_2$-groups recovered as the respective compound.)

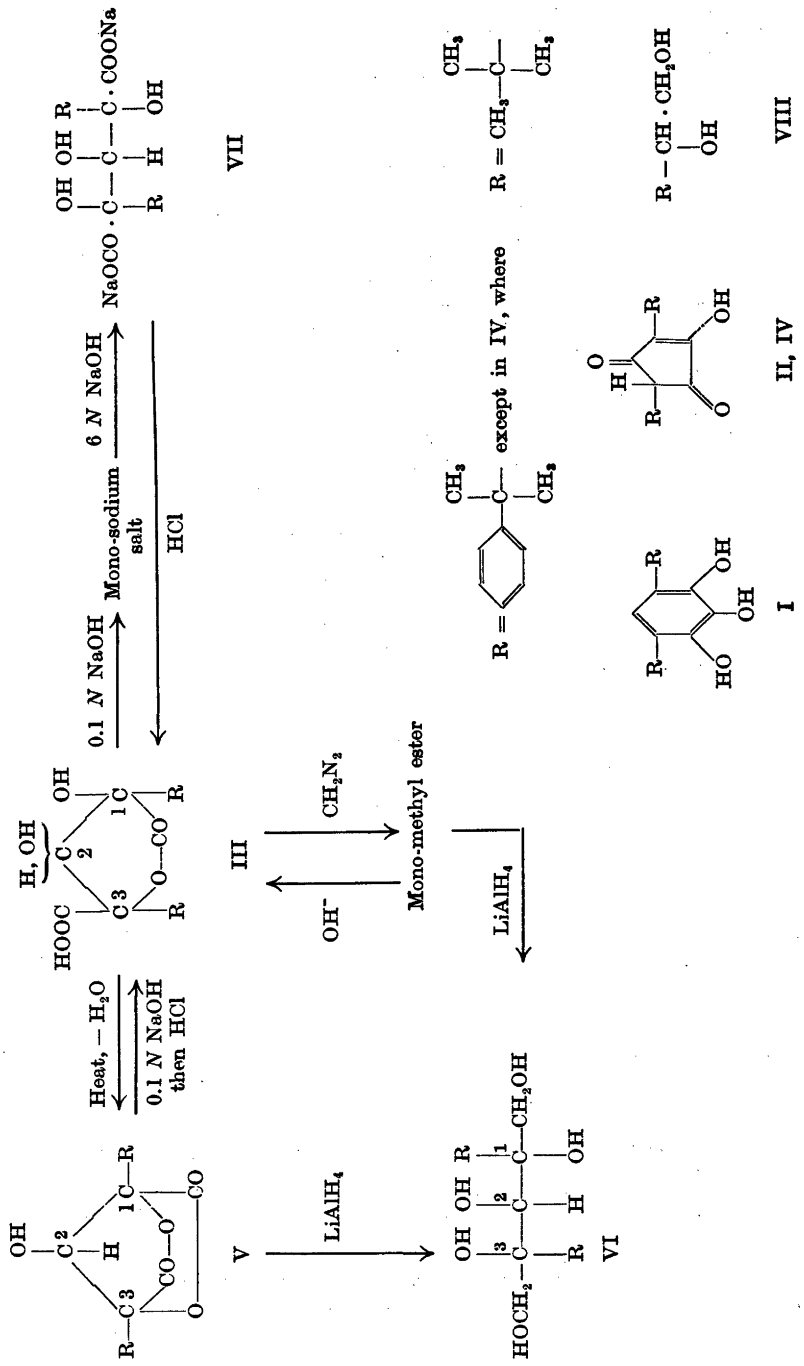
EXPERIMENTAL *

Investigation of compound A, m.p. 174—175°

Compound A was isolated as described earlier [1]. The substance was obtained as colourless needles, m. p. 174—175°, with the composition $C_{23}H_{24}O_3$. (Found: C 79.4; H 7.00; neutr. equiv. 347. $C_{23}H_{24}O_3$ requires: C 79.3; H 6.94; neutr.equiv. 348.4.) It was insoluble in sodium bicarbonate solution but dissolved readily in *N* sodium hydroxide. It gave an intense crimson colouration with ferric chloride, but did not react with hydroxylamine or 2,4-dinitrophenylhydrazine.

Cyclohexylammonium salt. On addition of excess *cyclo*hexylamine to an ethereal solution of A a mono *cyclo*hexylammonium salt separated. Needles from ethanol, m. p. 186—188° (decomp.) (Found: N 3.10. $C_{29}H_{37}NO_3$ requires: N 3.13.)

* All melting points uncorrected. Petrol refers to the fraction b.p. 40—60°.


Heat, – H2O
0.1 N NaOH then HCl
V
LiAlH4
VI
III
CH2N2
OH⁻
Mono-methyl ester
LiAlH4
0.1 N NaOH
Mono-sodium salt
6 N NaOH
HCl
VII
except in IV, where
R =
R = CH3
II, IV
I
VIII

Methyl ether. Treatment of A in methanol with an excess of dimethyl sulphate and alkali gave a high yield of a neutral monomethyl ether. Needles from petrol, m. p. 72.5—73.5°. (Found: C 80.2; H 7.28; CH_3O 8.57. $C_{24}H_{26}O_3$ requires: C 79.5; H 7.23; CH_3O 8.56.) The compound gave no colouration with ferric chloride.

Investigation of compound B, m.p. 185—186°

Compound B was isolated as described earlier [1] and obtained as colourless needles from ethanol, m. p. 185—186°, with the composition $C_{22}H_{26}O_6$. (Found: C 69.2, 69.0; H 6.20, 6.55; neutr.equiv. 397/phenolphthalein. $C_{22}H_{26}O_6$ requires: C 69.3; H 6.58; neutr. equiv. 398.4.) The compound was insoluble in water, sparingly soluble in hot benzene and readily so in hot ethanol. It gave a positive hydroxamate test for ester groups and a yellow precipitate with ferric chloride.

Cyclohexylammonium salt. When an excess *cyclo*hexylamine was added to an alcoholic solution of B a mono-*cyclo*hexylammonium salt separated as long, thin needles. M. p. 213—215° (decomp.). (Found: C 69.8; H 8.21; N 2.74. $C_{28}H_{39}NO_6$ requires: C 70.0; H 8.20; N 2.82.)

Piperidinium salt. This salt was similarly prepared from B and piperidine in ethanol. Needles, which melted at 141—143°, resolidified at about 170° and then melted at 225—228°, or rhombic plates, m. p. 225—228°. (Found: C 69.4; H 7.67; N 2.85. $C_{26}H_{37}NO_6$ requires: C 69.5; H 7.71; N 2.90.)

Disodium salt. When B (1.0 g) was dissolved in the minimum amount of hot *N* sodium hydroxide, and the solution was added to boiling 6 *N* sodium hydroxide (25 ml) a disodium salt soon started to separate. After cooling the salt was filtered off, rapidly washed with ice-cold water, acetone and ether and dried. (Found: C 58.6; H 6.1; Na 10.2; neutr. equiv. 462. $C_{25}H_{26}O_7Na_2$ requires: C 60.0; H 5.7; Na 10.0; neutr. equiv. 460.4.) The neutralisation equivalent of the salt was determined by dissolving the compound in aqueous ethanol, adding standard 0.1 *N* hydrochloric acid and titrating the excess acid with 0.1 *N* sodium hydroxide, using phenolphthalein as indicator. — When an aqueous solution of this salt was acidified with hydrochloric acid compound B separated (identified by mixed m. p.).

Methyl ester of B. When an ethereal solution of III was left overnight with an excess diazomethane a monomethyl ester formed. Needles from benzene-petrol. M. p. 162°. (Found: C 69.9; H 7.10; CH_3O 7.6. $C_{24}H_{28}O_6$ requires: C 69.9; H 6.84; CH_3O 7.5.) The ester gave no colouration with ferric chloride. When refluxed with 2 *N* aqueous-ethanolic sodium hydroxide it was hydrolysed, and the acid B separated on acidification of the solution.

Dehydration of compound B. Compound B (3.0 g) was heated in a test tube inserted in an oil bath kept at 190—200° until the evolution of vapour ceased. The reaction product was crystallised from benzene-petrol. Needles (2.3 g), m. p. 187—187.5°. (Found: C 73.0; H 6.28; "active H" 0.8. $C_{22}H_{24}O_5$ requires: C 72.6; H 6.30.) In 0.1 *N* aqueous sodium hydroxide the compound slowly consumed alkali and dissolved. (Found: neutr. equiv. 384. Calculated: 380.4.)

Reduction of the methyl ester of B with lithium-aluminium hydride. The ester (3.0 g) in absolute ether (75 ml) was added with stirring to a suspension of lithium-aluminium hydride (2 g) in absolute ether (50 ml) and the mixture was refluxed overnight on the water bath. Excess hydride was destroyed by careful addition of water and the precipitated salts were dissolved with 4 *N* hydrochloric acid. The ether layer, containing the suspended reaction product, was separated from the aqueous solution, and the solid filtered off and crystallised from aqueous ethanol. Colourless needles (2.1 g) m. p. 163—164°. (Found: C 71.6; H 8.01. $C_{22}H_{32}O_5$ requires: C 71.1; H 8.30.) The compound was almost insoluble in ether and water, readily soluble in ethanol. Gentle heating of the compound with concentrated sulphuric acid produced an intense red colouration. Attempts to acetylate the compound invariably led to mixtures.

Reduction of the dehydration product from B with lithium-aluminium hydride. When the dehydration product from B was treated as just described for the ester of B a polyol resulted, m. p. 163°, which was found by mixed melting point determination to be identical with the reduction product from this ester.

Oxidation of B with alkaline potassium permanganate. Compound B (2.5 g) was refluxed with a solution of potassium hydroxide (15 g) in water (50 ml) until a solid salt started to separate. Powdered potassium permanganate (25 g) was added and the mixture heated overnight on the water bath. Excess permanganate was destroyed with sulphur dioxide, the solution acidified with dilute sulphuric acid, and repeatedly extracted with ether. On evaporation of the ether a solid was obtained, which was crystallised once from petrol. Yield 1.2 g. Several crystallisations gave needles, m. p. 78° undepressed by *α*-phenyl*iso*-butyric acid.

D,L-*1,2-dihydroxy-3-methyl-3-phenylbutane* (VIII). Ethyl *α*-oxo-*β*-phenyl*iso*valerate (20 g) in absolute ether (50 ml) was added with stirring to a suspension of lithium-aluminium hydride (7.0 g) in absolute ether (100 ml). The mixture was refluxed overnight, excess hydride was destroyed by careful addition of water, and the precipitated salts were dissolved by addition of 6 *N* hydrochloric acid. The diol was extracted with ether, washed with water and sodium bicarbonate solution and the extract dried (K_2CO_3). Removal of the ether yielded an oil, which crystallised when cooled and scratched. Crystallisation from petrol afforded colourless needles (15.4 g), m. p. 50—51°. (Found: C 73.4; H 8.78. $C_{11}H_{16}O_2$ requires: C 73.3; H 8.95.) The compound consumed 1.0 mole of periodate when treated with periodic acid in dilute acetic acid.

The author wishes to acknowledge his indebtedness to *Statens Tekniska Forskningsråd* for a Fellowship, to *Cancernämnden* for financial support, to Miss E. Duintjer for skilful assistance and to Dr. K. E. Almin for running the infrared spectrum.

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Received November 1, 1954.