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Ozonolysis and Structure of Some Benzofurans

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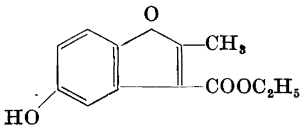
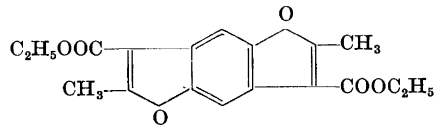
Stable, crystalline ozonides have been obtained by ozonisation of 2-methyl-3-carbethoxy-5-acetoxybenzofuran and 2,7-dimethyl-3-carbethoxy-5-acetoxybenzofuran. The structure of reaction products from toluquinone and ethyl acetoacetate and acetylacetone, respectively, has been determined. Further the ozonolysis of 2-methyl-3-carbethoxy-5-hydroxybenzofuran, 2-methyl-3-acetyl-5-hydroxybenzofuran and 2-methyl-3-acetyl-5-acetoxybenzofuran is described.

By the reaction between ethyl acetoacetate and *p*-benzoquinone in the presence of anhydrous zinc chloride there is formed a mixture of a benzofuran and a benzodifuran. The synthesis was first described by v. Pechmann [1] and Ikuta [2], the latter author providing the proof for the structures (I and II) of the products.



I



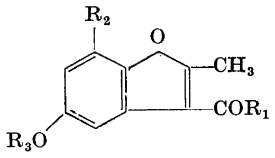
II

Some years later Graebe and Levy [3] extended the synthesis to include toluquinone and proposed a revision of some of Ikuta's structural formulae. These have, however, been corroborated by more recent work by Bernatek [4]. Further extensions of the synthesis have been made through the investigations of the latter [4–6] and by Grinev and his collaborators [7,8].

Ozonolysis of benzofurans was originally established by v. Wacek, Eppinger and v. Bezard [9] but the reaction seems not to have been exploited until some benzodifurans were ozonised by Bernatek and Thoresen [10] in 1955. That investigation was from the outset aimed at structural problems but as an interesting sideline it was found that when suitably substituted a benzodifuran would yield very stable and excellently crystallising ozonides.

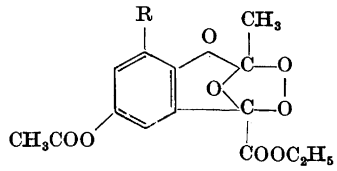
The present paper deals with the ozonolysis of I and III (a product from benzoquinone and acetylacetone) as well as their homologs IV and V contain-

ing a methyl group in the benzene ring. IV was prepared by Graebe and Levy but no attempts to determine the position of the methyl group were made at that time. Our interest is therefore in part directed towards structural problems and in part towards the possible formation of stable ozonides.



IA: $R_1 = OC_2H_5$, $R_2 = H$, $R_3 = CH_3CO$
III: $R_1 = CH_3$, $R_2 = R_3 = H$
IIIA: $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3CO$
IV: $R_1 = OC_2H_5$, $R_2 = CH_3$, $R_3 = H$
IVA: $R_1 = OC_2H_5$, $R_2 = CH_3$, $R_3 = CH_3CO$
V: $R_1 = R_2 = CH_3$, $R_3 = H$
VA: $R_1 = R_2 = CH_3$, $R_3 = CH_3CO$

The ozonolyses were performed in ethyl acetate at 0°. In order to isolate stable ozonides it was found necessary to ozonise the acetates rather than the free hydroxybenzofurans. Thus substance I gave no ozonide when concentrating the reaction mixture, but a yellow, peroxidic syrup which decomposed violently at room temperature. No definite decomposition products were isolated. It is believed that the presence of a free hydroxyl group enhances combustion of the molecule. IA on the other hand yielded a stable, monomeric ozonide $C_{14}H_{14}O_8$ (VI).

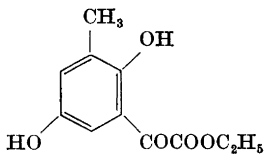


VI: R = H
VII: R = CH_3

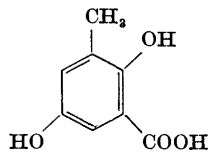
Ozonolysis of III gave a light brown syrup which was decomposed with aqueous sodium carbonate and acidified with hydrochloric acid. After several days in a refrigerator a small amount of crystals appeared and were identified as gentisic acid (hydroquinone carboxylic acid).

The immediate ozonisation product of IIIA was also a brownish, peroxidic syrup which was rather stable and may have contained an ozonide, but no such was isolated. After some time the syrup deposited white crystals of gentisic acid diacetate. From these results it is clear that the hydroxyl in III must be in *para*-position to the oxygen bridge of the furan ring. We have thus another support for the original formula of Ikuta in contrast to the proposals of Graebe and Levy where the hydroxyl and the oxygen bridge would have been in *meta*-position to each other.

IV gave after ozonisation a colourless syrup which decomposed slowly with evolution of gas. After some days white crystals separated which were identified as oxalic acid. The degradation had in this case evidently gone very far. IVA yielded as expected a stable ozonide $C_{15}H_{16}O_8$ (VII). On treatment with sodium iodide in glacial acetic acid it was reduced to a monoacetate of ethyl 2,5-dihydroxy-3-methylphenylglyoxalate (VIII).



VIII



IX

Whether the acetoxy group is attached to the 2- or 5-position cannot be proved conclusively, but the latter position is considered the more likely one. If the ozonide (VII) had been reduced without complications, the diacetate of VIII would have formed. During the reaction the new acetoxy group probably has been split off *in statu nascendi*. The acetate of VIII was boiled with glacial acetic acid and sodium acetate to give the free ketoacid. This was in turn oxidised with hydrogen peroxide and hydrolysed with hydrochloric acid to the methyl gentisic acid IX (2,5-dihydroxy-3-methyl-benzoic acid). Proof is hereby secured for the position of the methyl group *ortho* to the oxygen bridge in the reaction product from toluquinone and ethyl acetoacetate (IV).

Of V (the product from toluquinone and acetylacetone) only its acetate VA was ozonised. No ozonide was obtained from this compound but a peroxidic syrup which deposited crystals of 2,5-diacetoxy-3-methylbenzoic acid (diacetate of IX). The position of the methyl group in the benzene ring of V must consequently be the same as in IV.

Regarding the course of ozonolysis it is obvious that IA and IVA mainly undergo the normal reaction. The same probably holds true also for I and IV, but here the free hydroxyl group is responsible for a secondary and far-reaching decomposition. III, IIIA and VA all lose their 3-acetyl groups which is consistent with an anomalous ozonolysis. The fact that the peroxidic syrups resulting from the ozonisation had any stability at all at room temperature, however, makes it more probable that the ozonisation proper was a normal one and followed by a rearrangement.

EXPERIMENTAL

(Melting points not corrected)

Ozonisation procedure. The substance was usually dissolved in about 50 times its weight of pure ethyl acetate and the solution cooled in an ice-bath. A current of oxygen containing 4.5 % (wt) of ozone was passed through the solution at a rate of 30 l/h. Some ozone always escaped from the reaction mixture and the reagent was therefore passed through in excess of the calculated amount. The ozonised solution was concentrated *in vacuo* and worked up as described below.

2-Methyl-3-carbethoxy-5-hydroxybenzofuran (I) and its acetate (IA). I (3.0 g) in ethyl acetate (150 ml) was ozonised for 60 min. During the reaction a strong yellow colour appeared but vanished towards the end. After concentration *in vacuo* at room temperature a yellow syrup remained which almost immediately decomposed violently.

IA (3.0 g) in ethyl acetate (150 ml) was ozonised for 60 min. Transitory yellow colour. After concentration a yellow syrup remained which crystallised after two days in a refrigerator. Recrystallised from ethanol, m. p. 105° (1.2 g). (Found: C 54.2; H 4.7; act. O 5.2; M (benzene) 290. Calc. for $C_{14}H_{14}O_8$: C 54.2; H 4.6; act. O 5.2; M 310.)

2-Methyl-3-acetyl-5-hydroxybenzofuran (II) and its acetate (IIA). II (2.5 g) in ethyl acetate (100 ml) was ozonised for 30 min. Transitory yellow colour. After concentration the brownish syrup did not crystallise after one week in a refrigerator. The syrup was treated with aqueous sodium carbonate until a clear solution remained. Upon acidification white crystals slowly began to separate. Recrystallised from a small amount of water, m. p. 199°. Mixed m. p. with an authentic sample of gentisic acid showed no depression. IIA (3 g) in ethyl acetate (150 ml) was ozonised for 60 min. Concentration gave a brownish syrup which after being kept in a refrigerator overnight deposited white crystals. Recrystallised from ethyl acetate-petrol ether m. p. 122° (0.35 g). Mixed m. p. with an authentic sample of diacetylgentisic acid (m. p. 119°) showed no depression. (Found: C 55.5; H 4.1; E 237. Calc. for $C_{11}H_{10}O_6$: C 55.5; H 4.2; E 238.)

2,7-Dimethyl-3-carbethoxy-5-hydroxybenzofuran (IV) and its acetate (IVA). IV (1.5 g) in ethyl acetate (75 ml) was ozonised for 30 min. Concentration *in vacuo* afforded a syrup which at room temperature underwent a slow decomposition with evolution of gas. After two days in a refrigerator white crystals separated. Recrystallised from water, m. p. *ca.* 102° (0.05 g). Mixed m. p. with oxalic acid was undepressed. (Found: C 19.2; H 4.9. Calc. for $C_2H_2O_4 \cdot 2H_2O$: C 19.1; H 4.8).

IVA (2.5 g) in ethyl acetate (150 ml) was ozonised for 60 min. During concentration a yellowish substance separated. M. p. 109—111° (1.7 g). Recrystallised from ethanol, m. p. 112°. (Found: C 55.6; H 5.0; act. O 4.9. Calc. fo · $C_{15}H_{16}O_8$: C 55.6; H 5.0; act. O 5.0.) The ozonide (VII) (0.8 g) was treated overnight with sodium iodide (0.75 g) in glacial acetic acid and the liberated iodine removed with aqueous sodium sulphite. A yellow oil separated and crystallised on scratching. Recrystallised from dilute ethanol, yellowish needles of m. p. 69°, gave an orange-coloured precipitate with 2,4-dinitrophenylhydrazine. (Found: C 58.6; H 5.3. Calc. for $C_{13}H_{14}O_6$: C 58.6; H 5.3.)

$C_{13}H_{14}O_6$ (monoacetate of VIII) (0.20 g), anhydrous sodium acetate (0.25 g) and glacial acetic acid (5 ml) were refluxed for one hour and evaporated to dryness *in vacuo*. The yellow residue (sodium salt) was taken up in water and acidified with hydrochloric acid when a yellow substance separated. Recrystallised from benzene, yellow-orange needles, m. p. 132° (0.15 g). Red precipitate with 2,4-dinitrophenylhydrazine. (Found: C 55.4; H 4.6. Calc. for $C_{11}H_{10}O_6$: C 55.5; H 4.2.)

The ketoacid $C_{11}H_{10}O_6$ (0.15 g) and hydrogen peroxide (5 ml, 1 %) were stirred at room temperature for 2 h and left for another 17 h. The yellow colour had disappeared and a white substance separated. Recrystallised from ethyl acetate-ligroin and from dilute ethanol, m. p. 146°. This substance was refluxed with hydrochloric acid (5 ml, 1 N) for 30 min. On cooling yellowish needles separated. Recrystallised from a small amount of water. White needles, m. p. 216°. Mixed m. p. with an authentic sample of 2,5-dihydroxy-3-methylbenzoic acid (prepared from *o*-cresotic acid by persulphate oxidation [11]) showed no depression. Also the I.R.-spectra of the two samples were identical.

2,7-Dimethyl-3-acetyl-5-hydroxybenzofuran (V) and its acetate (VA). To a mixture of acetylacetone (8 ml), acetone (30 ml) and anhydrous zinc chloride (11 g) was added toluquinone (4 g) in small portions. The mixture was refluxed for 30 min and on cooling a white substance separated. Recrystallized from acetone, m. p. 235° (4 g). The red colour characteristic for benzofurans was produced by heating with concentrated sulphuric acid. With 2,4-dinitrophenylhydrazine a red substance was formed, m. p. 255°. (Found: C 70.7; H 5.9. Calc. for $C_{12}H_{12}O_3$: C 70.6; H 5.9.)

V (3 g) in acetyl chloride (15 ml) was refluxed for 15 min. The mixture was poured into 600 ml of ice-water and stirred vigorously. The separated substance was washed thoroughly and recrystallised from 50 % ethanol, 2.7 g, m. p. 97°. (Found: C 68.2; H 5.6. Calc. for $C_{14}H_{14}O_4$: C 68.3; H 5.7.)

VA (2.7 g) in ethyl acetate (150 ml) was ozonised for 60 min. On concentration a light yellow syrup remained which after some days in a refrigerator deposited a white substance. Recrystallised from ethyl acetate-ligroin and from dilute ethanol, m. p. 148°. (Found: C 57.0; H 4.7; E 252. Calc. for $C_{12}H_{12}O_6$: C 57.2; H 4.8; E 251.) Mixed m. p. with an authentic sample of 2,5-diacetoxy-3-methylbenzoic acid was undepressed. Also the I.R.-spectra of the two compounds were identical.

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