ACTA CHEMICA SCANDINAVICA 9 (1955) 743—748

Ozonization of Some Benzodifurans

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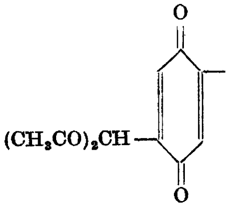
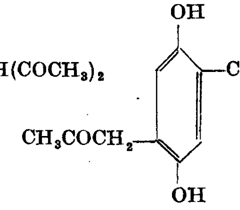
Three derivatives of benzo [1.2-b, 4.5-b′] difuran have been ozonized. Ozone was rapidly added to the furan double bonds. The products of decomposition are discussed. In one instance remarkably stable and well-crystallizing ozonides were obtained.

The base-catalyzed reaction of acetylacetone with *p*-benzoquinone led, as found by one of the present authors [1,2], to the new compound $\omega, \omega, \omega', \omega'$-tetraacetyl-*p*-xyloquinone (I).



I



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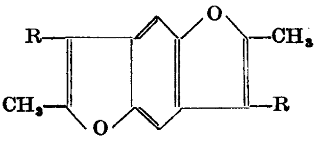


III

On catalytic hydrogenation in methanol this substance gave, with simultaneous loss of two acetyl groups, ω, ω'-diacetyl-*p*-xylohydroquinone (II) which in turn by treatment with acetyl chloride would split off two molecules of water and thereby effect a ring closure to 2,6-dimethylbenzo [1.2-b, 4.5-b′]-difuran (III, R = H). Another route to III (R = H) was found in condensing ethyl acetoacetate and *p*-benzoquinone to ethyl 2,6-dimethylbenzo [1.2-b,-4.5-b′]-difuran-3,7-dicarboxylate (III, R = $COOC_2H_5$) as described by v. Pechmann [3] and Ikuta [4]. Hydrolysis of this ester and decarboxylation of the corresponding potassium salt furnished a substance identical with III (R = H).

Most of our arguments in favor of the structure III (R = H) were thus based upon an acceptance of the correctness of the structural formulae put forward by Ikuta [4]. However sound this foundation may be it was felt that some independent proof ought to be furnished.

Several modes of degradation were contemplated and that of ozonolysis chosen as the most promising. v. Wacek, Eppinger and v. Bézard[5] have carried out ozonization of benzofuran and some homologues with the substituents in the furan ring. Their experiments indicate a facile reaction with the furan double bond without any noticeable attack on the benzene nucleus. Further the yield of the expected aldehydes seems to be reasonably good and not too susceptible to the method of decomposing the ozonide.

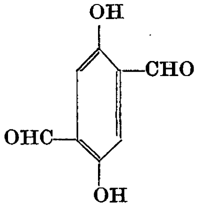
III (R = H) was ozonized in chloroform or glacial acetic acid at room temperature with 3 to 4 % ozone. Ozone was rapidly absorbed during the first half of the reaction but escaped thereafter in increasing amounts. This is of course in agreement with the well-established fact that in a conjugated system (the two furan double bonds are conjugated through the benzene nucleus) where no aromatic bonds are attacked by ozone, addition occurs much more rapidly to the first double bond than to subsequent ones.

When the calculated amount of ozone had been passed into the solution decomposition was effected in two ways:

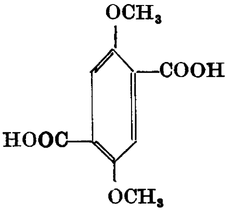
A The chloroform solutions were concentrated *in vacuo* until a syrupy ozonide remained. This was decomposed with hot water.
B Zinc dust was added to the glacial acetic acid solutions and the mixtures heated on a water-bath.

In both instances hydroquinone-2,5-dialdehyde (or 2,5-dihydroxyterephthalaldehyde) (IV) was obtained in 15 to 20 % yield. Other decomposition products (acids and polyvalent phenols) evaded isolation and identification.

The dialdehyde IV could be acetylated to give a diacetylderivative and reacted with *p*-nitrophenylhydrazine to give a bis(*p*-nitrophenylhydrazone). With methyl sulphate in alkaline solution it was converted into 2,5-dimethoxyterephthalaldehyde which could be oxidized by permanganate to 2,5-dimethoxyterephthalic acid (V).

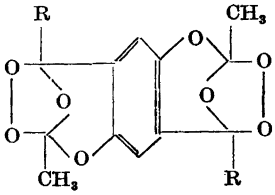


IV

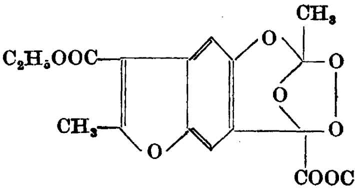


V

We considered it of interest also to try the ozonization reaction on two other available benzodifurans, *viz.* the beforementioned ethyl 2,6-dimethylbenzo-[1.2-b, 4.5-b']difuran-3,7-dicarboxylate (III, R = $COOC_2H_5$) and 2,6-dimethyl-3,7-diacetylbenzo-[1.2-b,4.5-b']difuran (III, R = $COCH_3$). III (R = $COOC_2H_5$) was ozonized in ethyl acetate and the solution concentrated *in vacuo*. The resulting syrup was interspersed with white crystals. On treatment with a small amount of ethanol these were left undissolved while the syrup went into solution. When the ethanolic solution was concentrated a second and smaller crop of the white crystals separated. The filtrate was slowly concentrated further when beautiful yellow crystals were formed. The mother liquor was then a reddish syrup from which no more crystalline material could be obtained. Most likely the two crystalline substances were ozonides as they burned in a flame with the typical vigour and contained active oxygen. Analysis gave the composition $C_{18}H_{18}O_{12}$ with two active oxygens for the white compound and $C_{18}H_{18}O_9$ with one active oxygen for the yellow compound. The former must have the structure VI (R = $COOC_2H_5$) and the latter the structure VII representing a diozonide and monozonide, respectively. Determination of the molecular weights showed both ozonides to be monomeric. VI (R = $COOC_2H_5$) and VII could be recrystallized from hot alcohol or from glacial acetic acid and have now been kept for a long time at room temperature without noticeable decomposition. They are consequently of a stability rarely encountered in true ozonides of non-nitrogenous heterocycles [6].

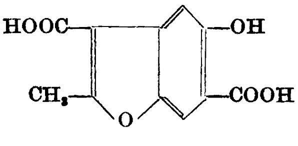


VI

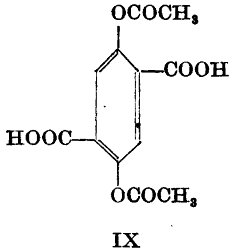


VII

Catalytically activated hydrogen was readily absorbed by the ozonides but only dark tarry syrups resulted from the reaction. Boiled with aqueous sodium hydroxide, VI (R = $COOC_2H_5$) was hydrolyzed to 2,5-dihydroxyterephthalic acid which was identified as the dimethyl ether (V). Under the same conditions VII yielded a dibasic acid $C_{11}H_8O_6$ which, when heated with concentrated sulphuric acid, gave the violet colour typical for benzofurans. The structure VIII was assigned to this substance whose dimethyl ester was prepared by the action of diazomethane.



VIII



IX

2,6-Dimethyl-3,7-diacetylbenzo[1.2-b, 4.5-b]difuran (III, R = $COCH_3$) was also ozonized in ethyl acetate. After evaporation of the solvent a clear yellow syrup remained. It was dissolved in a few ml of ethanol and the solution was concentrated by slow evaporation at room temperature. In the course of several days a light yellow substance separated which showed all signs of being an ozonide. It was, however, much less stable than VI (R = $COOC_2H_5$), being decomposed by hot ethanol for instance. No accurate analysis could be obtained but its content of active oxygen indicated that it must be the diozonide VI (R = $COCH_3$). Aqueous sodium carbonate hydrolyzed it to 2,5-dihydroxyterephthalic acid. The syrupy mother liquor from VI (R = $COCH_3$) was placed in a refrigerator when a new white substance separated. It was obviously an acid and when hydrolyzed in aqueous sodium carbonate it yielded 2,5-dihydroxyterephthalic acid. With diazomethane it gave 2,5-diacetoxyterephthalic acid dimethyl ester and must have the structure IX which is one of the decomposition products expected from the diozonide VI (R =$COCH_3$). The noncrystallizing syrup left when IX was removed furnished on hydrolysis a good yield of 2,5-dihydroxyterephthalic acid.

EXPERIMENTAL

(Melting points not corrected)

Ozonization of III (R = H)

III (R = H) (3 g) was dissolved in the appropriate solvent (chloroform or glacial acetic acid) (150 ml) and a current of oxygen (*ca.* 30 l h^{-1}) containing 4.5 % (wt.) ozone was passed through the solution until the calculated amount plus 40 % was absorbed. Unabsorbed ozone in the exit gas was measured from time to time by reaction with aqueous potassium iodide. The 40 % excess is supposed approximately to make up for the amount of ozone decomposed by the solvent before reacting with the benzodifuran. Reaction temperature was 0° with chloroform as a solvent and room temperature with glacial acetic acid.

Decomposition with hot water: The chloroform was removed *in vacuo* at 20°. The residue was a viscous yellow syrup, burning explosively and containing active oxygen. Due to insuperable difficulties in purification of the ozonide the content of active oxygen was not determined. After adding water the mixture was heated on a water-bath for 30 to 45 minutes. The resulting reddish-brown solution was allowed to cool when a brown substance separated. This heterogenous mixture was exhaustively extracted with ether. The combined extracts were shaken with a saturated solution of sodium hydrogen carbonate until the evolution of carbon dioxide had ceased. On acidifying this solution yielded a yellowish-brown substance which could not be identified. By now the ethereal solution had a clean yellow colour and after drying it was concentrated to a small volume when a crystalline yellow substance separated (IV).

Reductive decomposition: To the glacial acetic acid solution zinc dust was added and the mixture heated on a water-bath for 30 to 45 minutes with occasional stirring. The reddish-brown solution was filtered and evaporated to dryness *in vacuo*. Extraction with ether gave a solution which was treated as in the above experiment. The yield of the yellow substance (IV) was roughly the same (0.4—0.5 g) in both cases.

IV dissolved in alkali with an intense violet colour, gave a blue-violet colour with ferric chloride and reduced Tollen's reagent in the cold. It was not very volatile in steam. Recrystallized from benzene it decomposed at 240—245°. (Found: C 58.19; H 3.71. Calc. for $C_8H_6O_4$: C 57.83; H 3.64.

Acetylation: IV (79 mg) was refluxed with acetyl chloride (20 ml) until the solution was colourless (*ca.* 3 hours) and then poured cautiously into ice-water containing some sodium hydrogen carbonate and stirred briskly. The precipitated white substance (110 mg) was filtered off immediately and recrystallized from ligroin. White needles with m. p. 122—123°. In water or ethanol the substance seemed to decompose rapidly giving a yellow colour. (Found: C 57.48; H 4.11. Calc. for $C_{12}H_{10}O_6$: C 57.60; H 4.03.)

p-Nitrophenylhydrazone: To a hot solution of IV (0.5 g) in ethanol (35 ml) was added *p*-nitrophenylhydrazine (1.5 g) in ethanol (100 ml) and glacial acetic acid (5 ml). The mixture was heated on a water-bath for 30 minutes and the separated substance (0.95 g) filtered off. Recrystallized once from nitrobenzene and twice from glacial acetic acid and dried *in vacuo* at 100° over KOH for some 10 hours. Decomposed above 310° without melting. (Found: C 54.99; H 3.77; N 18.3. Calc. for $C_{20}H_{16}N_6O_6$: C 55.04; H 3.70; N 19.26.)

Methylation: IV (1 g) was dissolved in aqueous sodium hydroxide (10.5 ml, 1 *N*). To this solution was added methyl sulphate (1.1 ml) and the mixture shaken well. Methyl sulphate (1 ml) and sodium hydroxide (10 ml, 1 *N*) were added four times with shaking between each addition. Unreacted methyl sulphate was then decomposed with excess sodium hydroxide at room temperature. The separated substance (0.35 g) was washed repeatedly with water and recrystallized from ethanol. M. p. 205—206° dec. (Found: C 61.70; H 5.28; OCH_3 31.00. Calc. for $C_8H_4O_2(CH_3O)_2$: C 61.85; H 5.20; OCH_3 31.97.)

Oxidation of the above substance to V: The methyl ether (0.38 g) was suspended in aqueous sodium carbonate (10 ml, 2 *N*) and heated on a water-bath. Aqueous potassium permanganate (28 ml, 2.5 %) was added in small portions with mechanical stirring. Excess permanganate was destroyed with a few drops of ethanol. The filtered solution was acidified and concentrated when a small amount of yellow needles separated. M. p. 266° (Kofler bench), mixed m. p. with an authentic sample of 2,5-dimethoxyterephthalic acid showed no depression.

Ozonization of ethyl 2,6-dimethylbenzo [1.2-b, 4.5-b′]-difuran-3,7 dicarboxylate (III, $R = COOC_2H_5$)

III ($R = COOC_2H_5$) (4 g) was suspended in ethyl acetate (200 ml) and ozonized at room temperature with 2.9 % ozone at a rate of 30 lh^{-1} in 80 minutes. After 60 minutes the ester had dissolved. The solvent was evaporated *in vacuo* at 20° and the resulting mixture of a yellowish-brown syrup and white crystals was treated with a small amount of ethanol. The undissolved white crystals (1.2 g) were recrystallized from ethanol. M. p. 132—134° dec. with evolution of gas. (Found: C 50.69; H 4.36; act.O 7.34. Calc. for $C_{18}H_{18}O_{12}$ (426): C 50.72; H 4.26; act.O[7] 7.51.)

0.229 g subst. in acetone (11.97 g) $\Delta t = 0.08°$ $M = 409$

Hydrolysis of the above substance (VI, $R = COOC_2H_5$): The ozonide (1.62 g) was boiled with aqueous sodium hydroxide (40 ml, 1 *N*) for 30 minutes. After acidifying the dark solution, the separated yellow substance (0.65 g) was recrystallized from water (charcoal). The yellow needles decomposed above 300°. (Found: C 48.61; H 3.04; Equiv. wt. 97 (0.1 *N* NaOH, phenolphthalein). Calc. for $C_8H_6O_6$: C 48.51; H 3.05; Equiv. wt. for dibasic acid 99.)

$C_8H_6O_6$ was methylated in the usual way with methyl sulphate. The resulting ether had, after recrystallization from water (charcoal), m. p. 270° (Kofler bench). Mixed melting point with an authentic sample of 2,5-dimethoxyterephthalic acid (of m. p. 266°): 268°.

Isolation of the monozonide (VII): The mother liquor from VI ($R = COOC_2H_5$) was left in an open dish for some days when yellow crystals separated (1.0 g). After recrystallization from dilute ethanol they had m. p. 115° dec. with evolution of gas. (Found: C 57.15; N 4.62; act.O 4.10; 0.406 g subst. in 9.59 g acetone, $\Delta t = 0.19°$; $M = 381$. Calc. for $C_{18}H_{18}O_9$ (378): C 57.17; H 4.80; act.O[7] 4.23.)

Hydrolysis of VII: VII (0.92 g) was treated with aqueous sodium hydroxide as described for VI ($R = COOC_2H_5$). The product (0.42 g) was recrystallized from ethanol (charcoal) and had m. p. 312—313° dec. (Found: C 55.97; H 3.52; Equiv. wt. 115. Calc. for $C_{11}H_8O_6$: C 55.93; H 3.41; Equiv. wt. for dibasic acid 118.)

Methyl ester of VIII: VIII (0.5 g) was esterified by means of diazomethane (from 1.8 g of nitrosomethylurea) and the product (0.55 g) recrystallized from ethanol. Yellow needles. M. p. 176°. Found: C 59.05; H 4.72; OCH_3 23.06. Calc. for $C_{13}H_{12}O_6$: C 59.10; H 4.58; OCH_3 23.49.)

Ozonization of 2,6-dimethyl-3,7-diacetylbenzo [1.2-b, 4.5-b′]-difuran (III, $R = COCH_3$)

The benzodifuran (4.5 g) was suspended in ethyl acetate (200 ml) and ozonized at room temperature with 1.8 % ozone in 160 minutes. After evaporation of the solvent *in vacuo* the resulting yellow syrup was dissolved in a small amount of ethanol. This solution was concentrated somewhat and placed in a refrigerator for several days when a light yellow substance separated (79 mg). Could not be recrystallized as it easily decomposed. No melting point. At 155° (Kofler-bench) it decrepitated instantaneously, at lower temperatures a slow decomposition took place. The crude product was used for a determination of the contents of active oxygen. (Found: act.O 7.7. Calc. for $C_{16}H_{14}O_{10}$: act.O 8.7.)

Hydrolysis of VI ($R = COCH_3$): The ozonide (90 mg) was heated with sodium carbonate (5 ml, 1 *N*) for a few minutes. On acidifying yellow needles separated (45 mg) which, recrystallized from water, decomposed at *ca.* 330°. (Found: Equiv. wt. 98. Calc. for $C_6H_4O_2$ $(COOH)_2$: Equiv.wt. 99.)

2,5-Diacetoxyterephthalic acid (IX): The syrupy mother liquor from VI ($R = COCH_3$) was concentrated further and placed in a refrigerator when a white substance separated (400 mg). Recrystallized from benzene-ethanol it decomposed at ca. 260°. (Found: C 50.98; H 3.67. Calc. for $C_{12}H_{10}O_8$: C 51.07; H 3.57.)

Hydrolysis of IX: IX (100 mg) was boiled with aqueous sodium carbonate (10 ml, 1 *N*) for a few minutes. The solution which had become yellow was acidified and yellow needles separated (75 mg). Recrystallized from water they decomposed at 335°. (Found: Equiv.wt. 101. Calc. for $C_6H_4O_2(COOH)_2$: Equiv.wt. 99.)

Methyl ester of IX: IX (230 mg) was added to an ethereal solution of diazomethane. A white substance separated which recrystallized from ethanol had m. p. 166—168°. Mixed m. p. with an authentic sample of 2,6-diacetoxyterephthalic acid dimethyl ester showed no depression. (Found: C 54.10; H 4.60. Calc. for $C_{14}H_{14}O_8$: C 54.19; H 4.54.)

One of the authors (E. B.) wishes to express his gratitude to ***Fridtjof Nansens Fond*** for a grant.

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Received February 28, 1955.