[Contribution from the Institute of Organic Chemistry of the University of Szeged]

ADDITION OF MALEIC ANHYDRIDE TO ANETHOLE. II.

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In a previous paper we reported (1) that anethole with maleic anhydride forms a bis-adduct, the properties of which are in best agreement with the spatial formula I and naturally also with its enantiomorphic form. We can use as a simpler manner of design formula II which represents together the two enantiomorphic members of the racemate.

This formula is in close analogy with formula III which Wagner-Jauregg (2) first suggested for the bis-adduct formed by the addition of maleic anhydride to 1,1-diphenylethylene. The same formula was also accepted by Bergmann and co-workers (3), who even generalized it for other bis-adducts formed by the action of maleic anhydride on 1,1-diarylethylene derivatives, doing this in spite of the fact that they had not decisively proved the correctness of this formula. It is remarkable that in the meantime Wagner-Jauregg himself (4) had repudiated formula III. One of Wagner-Jauregg's essential arguments against the correctness of formula III was the failure of his efforts to prove the olefinic linkages revealed by this structure, *e.g.*, finding the bis-adduct resistant to catalytic hydrogenation. Indeed, we also observed that the olefinic bonds shown by our formula I could not be demonstrated by the simplest usual reactions for these linkages. So, *e.g.*, although the chloroform solution of our bis-adduct readily absorbs bromine (5), which is, however, finally due to a substitution, as we could isolate from the inhomogeneous oily reaction product only a very small amount of a crystalline product, containing at most one atom of bromine per mole of the initial substance; our bis-adduct does not give a color reaction with tetranitromethane, and resists catalytic hydrogenation (Pt or Pd) at atmospheric pressure.[1]

In spite of these negative results, we finally succeeded in a different way in showing both the olefinic bonds revealed by our formula I. Thus, the correctness of this formula is only now completely proved, because in our earlier paper (1) no argument was advanced in favor of the olefinic bond not belonging to the enol ether group.

The presence and position of one of the two olefinic bonds was proved earlier by the enol ether character of the bis-adduct. We tried first to locate the other olefinic bond by bromination of the hydroxy lactone tricarboxylic acid ("B-acid", IV) obtained from the bis-adduct. We found that IV, treated in aqueous solution with potassium hypobromite, or in methanolic solution with bromine, gave a monobromo product, yielding with diazomethane a monobromo tetramethyl ester[2] (m.p. 242°) for which we must accept formula Vb. It is therefore clear that the initially-formed dibromo addition product instantly loses one mole

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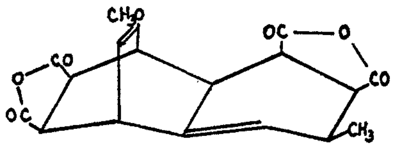
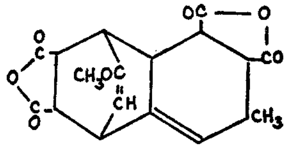
[1] No experiments were made under pressure.

[2] As shown in our previous paper (1) on the action of diazomethane, the lactone ring of IV split off, yielding the keto tetracarboxylic acid tetramethyl ester Va.

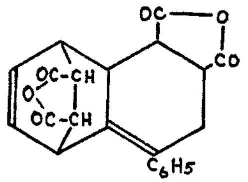
of hydrogen bromide, which leads to the formation of Vb. As the selective bromination by bromosuccinimide (6) of ester Va leads to another monobromotetracarboxylic keto acid tetramethyl ester (m.p. 153–158°, obviously Vc) than that mentioned above, it follows that free bromine did not act as a substituent on one of the hydrogen atoms attached to the neighboring carbon atom of the lactonized or free carbonyl group.



I



II



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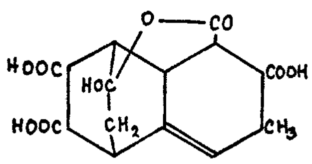
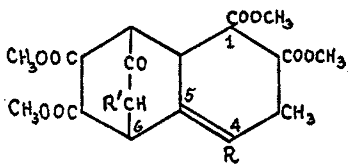


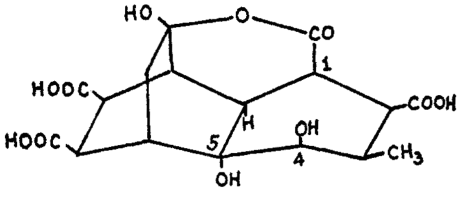
IV



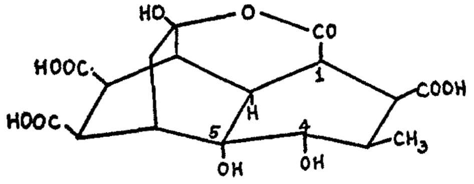
V

a. $R = R' = H$
b. $R = Br, R' = H$
c. $R = H, R' = Br$

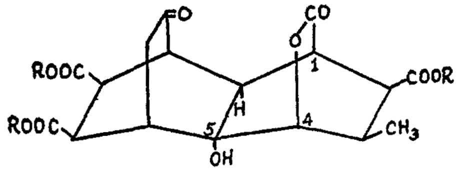
The olefinic linkage of IV and Va could be more clearly demonstrated by the products obtained through conversion with hydrogen peroxide. However, we found here a phenomenon of isomerism, whose exact explanation needs further investigation. On study of spatial models, we came to the conclusion that the addition of two hydroxyl groups to IV is only possible in the manner shown by formulas VI and VII, *i.e.*, the hydroxyl group in position 5 must have a trans position in relation to the carboxyl groups, whereas the hydroxyl group in position 4 can be either in a cis (VI) or a trans (VII) position. The only possibility for the trans position of the hydroxyl group attached to carbon atom 5 results from the fact that the endo-ethylene bridge permits only the existence of a cis-decalin type. It is to be expected that VI can easily, even spontaneously, undergo a rearrangement, followed by an intramolecular condensation leading to VIIIa. Indeed, we found that in acetic acid medium, on the action of hydrogen peroxide, from IV ($C_{17}H_{18}O_9$) the product $C_{17}H_{18}O_{10}$, m.p. 327–330°, is formed, in the sense of equation: $C_{17}H_{18}O_9 + H_2O_2 = C_{17}H_{18}O_{10} + H_2O$. This product, which is sparingly soluble in water and almost insoluble in the usual organic solvents, behaves on direct titration like a tribasic acid, corresponding to the lactonic character shown in formula VIIIa. Likewise, in the sense of equation $C_{21}H_{26}O_9 + H_2O_2 = C_{20}H_{24}O_{10} + CH_3OH$, treating Va ($C_{21}H_{26}O_9$) with hydrogen peroxide gave a neutral trimethyl ester (m.p. 265–270°), the analytical data of which agreed with those required by formula VIIIb. Actually, we could not decide whether this ester is the ester of the hydroxytricarboxylic keto acid VIIIa, for the latter could not be esterified because of its insolubility; on the other hand, the ester decomposed on saponification.



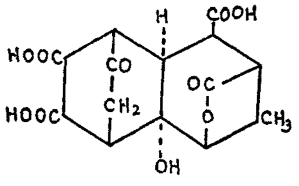
VI



VII



VIII. a. R=H; b. R=CH_3



IX

Furthermore, the conversion of IV with hydrogen peroxide led to still another product (m.p. 305–306°), in addition to the above-mentioned lactone. The analytical data of this other product agreed with those required by formula VI or VII ($C_{17}H_{20}O_{11}$). It was readily soluble, even in cold water, and behaved on direct titration like a tribasic acid. For this product formula VII can be excluded, as on treatment with diazomethane it did not form a tetramethyl ester[2] but led to a neutral trimethyl ester ($C_{20}H_{24}O_{10}$), whose identity with VIIIb (obtained from Va by treatment with hydrogen peroxide) could not be determined beyond doubt. It is possible that the structure of the easily-soluble product obtained by the action of hydrogen peroxide on IV is not the type of glycol corresponding to formula VI, but represents a lactone, or even a mixture of two isomeric lactones of formula $C_{17}H_{18}O_{10}$ containing one mole of crystal water. This is revealed by the fact that at 100° *in vacuo* it quickly loses one mole of water with destruction of its crystals, giving a hygroscopic substance. Concerning its structure, formula IX seems not to be probable, as such a ring structure would possess appreciable strain, so that the spontaneous lactonization could be explained only with difficulty.

The complete elucidation of the structures of both of the lactones mentioned above requires further investigation, the more so as it is possible that the easily-soluble lactone is a mixture of isomers. In spite of this, it is certain that the formation of the above-described substances shows the presence of an olefinic linkage in the initial compound. Thus, in IV the only unsaturated bond, and also two of them in the bis-adduct, are demonstrated.

EXPERIMENTAL

4-Bromo derivative of the keto tetracarboxylic acid tetramethyl ester Va (Vb). A. *From the B-acid (IV) with potassium hypobromite.* To a solution of 6.3 g. of bromine in 60 ml. of 10% aqueous solution of caustic soda, a solution of 3.64 g. of the B-acid (IV) in 200 ml. of a 2% aqueous solution of caustic soda was added. After standing for two days at room temperature, 88% of the active bromine was used up, and a negligible amount of precipitate appeared, which was filtered off. The filtrate was treated with sodium sulfite, then after acidifying (*p*H 1–2) with 2 *N* hydrochloric acid, evaporated *in vacuo* to dryness. The solid residue was twice boiled with 25 ml. of anhydrous methanol, and the solution thus obtained evaporated at reduced pressure. The yellow, oily residue crystallized from 20 ml. of water (charcoal) in colorless needles which were several times recrystallized from water, yielding 1.6 g. of a product containing bromine; m.p. 196°. As the analysis showed that this product consisted of a mixture of partially esterified derivatives of the monobromo acid, a sample (0.4 g.) was completely esterified by treatment of its anhydrous methanolic solution with diazomethane in the customary manner. The tetramethyl ester[2] thus obtained was recrystallized, first from methanol, then from ethyl acetate, yielding colorless needles, m.p. 237–238°. The substance contained bromine (Beilstein).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.
Found: C, 49.98, 50.15; H, 5.04, 4.99.

B. *From the B-acid (IV) with bromine in methanolic solution.* To a solution of 4 g. of the B-acid in 15 ml. of anhydrous methanol, 35 ml. of a 5% solution of bromine in anhydrous methanol was added. The color of the bromine disappeared in a few minutes. On evaporation, a yellowish oil was obtained, which after triturating with 12 ml. of water and standing for a few hours became mostly crystalline. After removing the supernatant aqueous layer, the oily-crystalline product was boiled for a few minutes with 100 ml. of water, then the small undissolved part filtered, and the filtrate, after concentration to 30 ml., allowed to stand at room temperature until crystallization became complete. Thus 1.1 g. of colorless needles was obtained which had the m.p. 183–184°. As analysis showed that this product consisted of a mixture of partially esterified derivatives of monobromo-IV, its total esterification was carried out using diazomethane. Thus, from 1 g. of the previously mentioned product, 0.7 g. of the same bromo trimethyl ester was obtained; m.p. 236–237°, which rose to 242° by recrystallization from ethyl acetate; m.p. of a mixture with a specimen obtained through method A, 238°. The substance contained bromine (Beilstein).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.
Found: C, 50.11; H, 5.22.

6^1-Bromo derivative of the keto tetracarboxylic acid tetramethyl ester Va (Vc). A solution of 1 g. of the ester Va and of 0.6 g. of bromosuccinimide in 60 ml. of tetrachloromethane was refluxed for 15 minutes, whereby precipitation of succinimide took place. On evaporating the filtrate an oily residue was obtained, which readily crystallized when triturated with cold methanol. The bromine-containing product was recrystallized from methanol, m.p. 153–158° (dec.).

Anal. Calc'd for $C_{21}H_{25}BrO_9$: C, 50.31; H, 5.01.
Found: C, 50.21; H, 5.25.

Reaction of the B-acid (IV) and of its methylated derivative (Va) with hydrogen peroxide. The sparingly soluble lactone (VIIIa). To a solution of 1.9 g. of the B-acid (IV) in 50 ml. of warm (80°) glacial acetic acid, 22 ml. of 33% hydrogen peroxide solution was added drop by drop within thirty minutes. The mixture was kept at 80° for another thirty minutes, then concentrated *in vacuo* to 6 ml. On standing for twelve hours, crystallization took place, yielding 1.5 g. of a colorless product, the main part of which dissolved on boiling for a short time with 10 ml. of water. The solution thus obtained contains the readily soluble lactone. The insoluble remainder was recrystallized once from 35 ml. of water. The colorless prisms showed no decomposition even on drying at 100° *in vacuo* over P_2O_5; yield 0.2 g., m.p. 327–330° (dec.). In the usual organic solvents the substance was practically insoluble even on boiling.

Anal. Calc'd for $C_{17}H_{18}O_{10}$: C, 53.40; H, 4.74.
Found: C, 53.58, 53.67; H, 4.88, 5.07.

Titration.[3] Calc'd for 3 COOH groups:[4] COOH, 35.34. Found: COOH, 34.95.

The readily-soluble lactone ($C_{17}H_{20}O_{11}$). After treatment with charcoal, the aqueous solution of the easily-soluble part of the crude reaction product previously described was kept in the ice-chest for some hours and the deposited prisms recrystallized twice from a small amount of water. For analysis, the substance was dried at room temperature in a desiccator over calcium chloride for twelve hours; no destruction of the crystals was observed; m.p. 305–306°.

Anal. Calc'd for $C_{17}H_{20}O_{11}$: C, 51.00; H, 5.03.
Found: C, 50.93, 50.86; H, 4.99, 5.23.

Titration.[3] Calc'd for 3 COOH groups:[4] COOH, 33.74. Found: COOH, 33.48.

On drying the substance (0.1 g.) *in vacuo* at 100° over P_2O_5, loss of one mole of water per mole of substance took place within two hours, accompanied by destruction of the crystals. The substance thus obtained was hygroscopic; on further drying, a slower loss of weight was observed.

Esterification of the readily-soluble lactone with diazomethane. A solution of 0.1 g. of the readily-soluble lactone in 2 ml. of anhydrous methanol was treated with diazomethane in the usual manner. On concentrating the solution to 0.5 ml., colorless prisms separated, which were recrystallized once from dilute methanol; m.p. 235–240°.

Anal. Calc'd for $C_{20}H_{24}O_{10}$: C, 56.58; H, 5.70.
Found: C, 56.62, 56.68; H, 5.87, 5.93.

Trimethyl ester VIIIb. To a solution of 2.1 g. of ester (Va) in 25 ml. of glacial acetic

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[3] All carboxyl estimations were carried out by direct titration of the hot alcoholic-aqueous solution of 30–50-mg. samples using 0.05 *N* sodium hydroxide and phenolphthalein.

[4] For the fourth (lactonized) carboxyl group, the lactone titrations did not give correct results, as the substance decomposed on boiling with dilute sodium hydroxide.

acid, 25 ml. of a 21% hydrogen peroxide solution was added, and the precipitate was redissolved by heating the mixture to 90°. After keeping the mixture at this temperature for ninety minutes, on cooling, 0.25 g. of colorless needles separated. On evaporating the filtrate at reduced pressure, an oily-crystalline residue was obtained, the oily part of which could be removed by solution in methanol. The crystalline residue (0.2 g.) proved to be identical with the primarily isolated crystal substance. The united crops were recrystallized from water, then dried *in vacuo* at 110°; m.p. 265–270° (dec.), after softening at 250°.

Anal. Calc'd for $C_{20}H_{24}O_{10}$: C, 56.58; H, 5.70.
Found: C, 56.76, 56.57; H, 5.93, 5.89.

Although the form of the crystals and their solubility seem to differ from those of the product obtained from the readily-soluble lactone by the action of diazomethane, it is possible that the two substances are identical, taking into account the possibility that they may consist of mixtures containing two isomeric lactones in different proportions. This conclusion can be deduced from the fact, that in spite of their correct analytical data, both products show unsharp m.p.'s, furthermore that their mixture melts at 236°, not showing a depression in relation to the lower-melting specimen. Accepting this conclusion, it follows that the readily-soluble lactone also consists of a mixture of isomers.

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