β-(*p*-Arsonophenyl)-isovaleric acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction with arsenic trioxide. The crude acid was purified by recrystallization from hot water; yield, 56 g. (75%).

Anal. Calcd. for $C_{11}H_{15}O_5As$: As, 24.85. Found: As, 24.38, 24.35.

β-(*p*-Arsenosophenyl)-isovaleric acid.—Forty grams of the above arsono acid was dissolved in a solution of 100 ml. of concentrated hydrochloric acid and 100 ml. of water. A small crystal of potassium iodide was added, and sulfur dioxide was passed through the solution for four and one-half hours. The solid which formed was collected and dissolved in sodium bicarbonate solution. Careful acidification with 10% hydrochloric acid precipitated the acid, which was collected and washed several times with cold water; yield, 9.2 g. The material was hygroscopic and analyzed for the hydrate.

Anal. Calcd. for $C_{11}H_{15}O_4As$: As, 26.14. Found: As, 26.83, 26.81.

β-(*p*-Hydroxyphenyl)-isovaleric Acid.—This acid was prepared from β-(*p*-aminophenyl)-isovaleric acid by the diazonium salt replacement reaction. Purification was best done by esterifying the crude acid with ethanol and sulfuric acid and taking advantage of the alkali solubility of the ester. Subsequent saponification and recrystallization of the acid from ethanol–ether–petroleum ether gave a white crystalline product melting at 146–148°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.04; H, 7.08.

Summary

The Friedel–Crafts addition of three halogenated benzenes to mesityl oxide to give 4-methyl-4-halogen substituted phenyl-2-pentanones is described.

A number of β-(*p*-substituted phenyl)-isovaleric acids are described.

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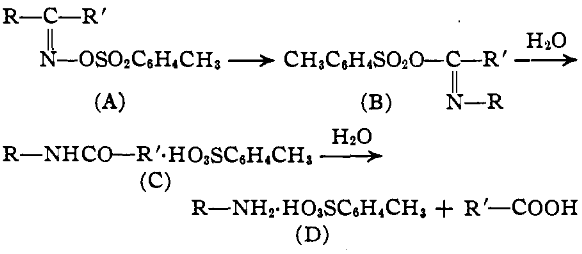
[CONTRIBUTION FROM THE ORGANIC CHEMICAL INSTITUTE OF THE HUNGARIAN UNIVERSITY "BOLYAI"]

Studies on Furan Compounds. I. Conversion of 2-Acetofuran to Hexen-2-dion-4,5-acetal-1 and Pyrocatechol

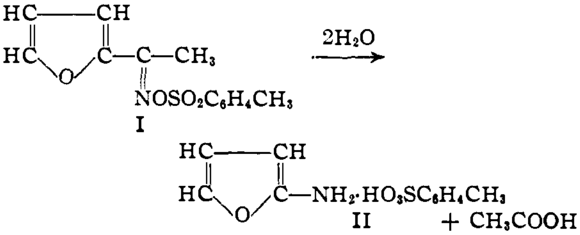
BY L. VARGHA, J. RAMONCZAI AND P. BITE

Several workers have already tried to synthesize 2-aminofuran. However, hydrolysis experiments on furan-2-ethylurethan[1] and on 2-benzyl- and 2-propionylaminofuran[2] have only resulted in the formation of ammonia and tar-like products, probably because 2-aminofuran decomposes very rapidly. We have thought that a milder procedure, such as the reaction discovered by Neber and v. Friedolfsheim[3] on the *p*-toluenesulfonyl derivatives of certain aromatic ketoximes (A) might lead to the desired goal. According to this process a compound like (A)



$$\underset{\text{(A)}}{\mathrm{R{-}\underset{\underset{\displaystyle N{-}OSO_2C_6H_4CH_3}{\|}}{C}{-}R'}} \longrightarrow \underset{\text{(B)}}{\mathrm{CH_3C_6H_4SO_2O{-}\underset{\underset{\displaystyle N{-}R}{\|}}{C}{-}R'}} \xrightarrow{H_2O} \underset{\text{(C)}}{\mathrm{R{-}NHCO{-}R'{\cdot}HO_3SC_6H_4CH_3}} \xrightarrow{H_2O} \underset{\text{(D)}}{\mathrm{R{-}NH_2{\cdot}HO_3SC_6H_4CH_3}} + \mathrm{R'{-}COOH}$$

when shaken with ethanol at room temperature, undergoes first a Beckmann rearrangement, then the intermediate (B) suffers hydrolytic cleavage (C) under the influence of traces of water with the eventual formation of an amine (D).[3,4]



I

II + CH_3COOH

$CH_3COCOCH{=}CHCH(OR)_2$
III, R = $-C_2H_5$
IV, R = $-CH_3$

$CH_3COCOCH_2CH_2CH(OR)_2$
V, R = $-C_2H_5$
VI, R = $-CH_3$

However, on shaking *p*-toluenesulfonyl 2-acetofuran oxime (I) with ethanol, not the expected toluenesulfonic acidic salt of 2-aminofuran (II) was obtained. Rather, we isolated, in addition to ammonium *p*-toluenesulfonate, a yellowish-green, strongly reducing liquid, which was free of nitrogen. Although very sensitive to heat, the liquid can be distilled *in vacuo* at constant temperature without being decomposed. The analysis and determination of molecular weight gave the elementary formula $C_{10}H_{16}O_4$ (III). Methanol, instead of ethanol, gave rise to a very similar substance with the formula $C_8H_{12}O_4$ (IV). These substances were found to represent *cis*-hexen-2-dion-4,5-diethylacetal-1 (III), and -dimethylacetal-1 (IV), respectively, as the end-products of the over-all reaction

$$\underset{\text{(I)}}{C_6H_6O{-}NOSO_2C_6H_4CH_3} + H_2O + 2ROH = CH_3C_6H_4SO_3(NH_4) + \text{III or IV}$$

Proof of the structures of III and IV rests on the following experimental facts.

With maleic anhydride no adduct originated[5] from III; therefore, the latter could not possess the furan nucleus. On catalytic hydrogenation

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(1) Leimbach, *J. prakt. Chem.*, [2], **65**, 20 (1902).

(2) Singleton and Edwards, THIS JOURNAL, **60**, 540 (1938).

(3) Neber and v. Friedolfsheim, *Ann.*, **449**, 109 (1926).

(4) Neber and Huh, *ibid.*, **515**, 292 (1935).

(5) Alder and Schmidt, *Ber.*, **76**, 18 (1943).

in the presence of palladium catalyst III and IV took up only one mole of hydrogen giving rise to two liquids with the elementary formulas of $C_{10}H_{18}O_4$ (V) and $C_8H_{14}O_4$ (VI), respectively whereas a furan compound would have required two moles of hydrogen at least. These experiments, therefore, indicated that the furan ring opened up during the reaction of I with alcohol, and that the substances (III, IV) so formed must be regarded as unsaturated aliphatic compounds.

In spite of the strong reduction shown toward ammoniacal silver nitrate or cold Fehling solution, substances III to VI could not contain free aldehyde groups because they gave positive test with fuchsin-sulfurous acid solution only after acid-catalyzed hydrolysis. Since the latter operation, beside one mole of acetic acid, yielded ethyl or methyl alcohol, it was concluded that each compound from III to VI contained an acetal grouping, which accounted for two atoms of oxygen in the empirical formulas. This conclusion was confirmed by the reactions of III and IV with aqueous hydroxylamine hydrochloride which gave rise to an identical oxime with the formula $C_6H_6O_2(=NOH)$. The fact that the latter substance was a true oxime was proved by benzoylation which produced the expected benzoyl ester, $C_6H_6O_2(=NOCOC_6H_5)$.

The remaining two oxygen atoms in III and IV were assumed to belong to two carbonyl groups, for no active hydrogen could be found in equivalent quantity according to Zerewitinow's method. The presence of one of these carbonyl groups could be demonstrated experimentally by the reaction of either III or IV with phenylhydrazine which led, under loss of two moles of alcohol, to an identical bisphenylhydrazone, $C_6H_6O(=NNHC_6H_5)_2$. The presence of the second carbonyl group could not be demonstrated in this reaction, because the substance suffered decomposition on prolonged heating with the carbonyl reagent.

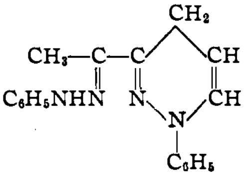
Final evidence of the correctness of structures III and IV was derived from the results of the oxidative degradations of these compounds. Thus it was found that, on treatment with ozone, compound IV gave rise to glyoxal which was isolated in form of its phenylosazone. This experiment proved that compound IV was essentially an unsaturated aldehyde, which contained its double bond between carbon atoms 2 and 3. Since oxidation of IV by potassium permanganate led to the formation of acetic acid and oxalic acid, the presence of an $CH_3CO—$ group in the molecule was indicated. This conclusion was in accord with the result of the acid-catalyzed hydrolysis of IV, which, instead of giving the expected unsaturated diketo-aldehyde, $CH_3COCOCH=CHCHO$, decomposed with formation of acetic acid and methyl alcohol. The correctness of structural formulas III to VI was also confirmed by other degradation reactions. Hollemann[6] and Böeseken[7] have shown that the oxidation of 1,2-diketones by hydrogen peroxide results in the corresponding acids, according to the reaction

$$R—COCO—R' + H_2O_2 = R—COOH + R'—COOH$$

By the application of this reaction in glacial acetic acid to IV, we obtained maleic acid, in consequence of the simultaneous hydrolysis of the acetal grouping and further oxidation of the free aldehyde to the acid

$$CH_3COCOCH=CH—CH(OCH_3)_2 \longrightarrow 2CH_3OH + CH_3COOH + [HOOC—CH=CH—CHO] \longrightarrow HOOC—CH=CH—COOH$$

These results confirmed not only the correctness of the established structural formulas for III to VI, but they also proved, because of the formation of maleic acid, the *cis*-configuration of III and IV, which could exist in two geometrical isomeric forms. The oxidation of the saturated compound VI by silver oxide in aqueous solution resulted in succinic acid, in accordance with the result obtained on the corresponding unsaturated compounds III and IV. The 1,4-relationship between the acetal group and one of the two carbonyl groups in compounds III to VI follows from the behavior of the saturated diketo-acetal VI toward phenylhydrazine. It is known from the literature[8] that 1,4-dicarbonyl compounds usually give rise to pyridazine derivatives. Accordingly, we have obtained from V or VI, on treatment with phenylhydrazine, a light-yellowish, crystalline powder which, on the basis of analysis, represents the phenylhydrazone of the 1-phenyl-3-acetodihydropyridazine (VII).



VII

In the course of our further work, we wished to study the free aldehydes, corresponding with the acetals III to VI. However, the unsaturated diketo-aldehyde, $CH_3COCOCH=CHCHO$, could not be produced by hydrolysis of III or IV, because, as already mentioned, the carbon-chain between the adjacent carbonyl groups split up with formation of acetic acid, even in cold aqueous solution. We attribute this easy cleavage of the carbon to carbon linkage in the dicarbonyl grouping to a loosening effect of the double bond which occupies an α,β-position.

The hydrolysis of the saturated acetals V and VI also led to a surprising result; because instead of the expected diketo-aldehyde (VIII), $CH_3COCOCH_2CH_2CHO$, there was produced pyrocatechol. The formation of the latter, however, can easily be explained through the trienol form (IX)

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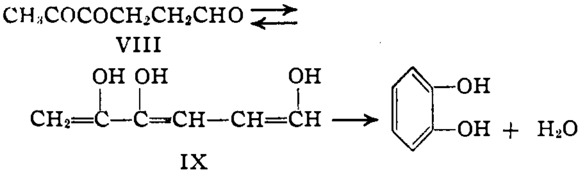
(6) Hollemann, *Rec. trav. chim.*, **23**, 169 (1904).

(7) Böeseken, *ibid.*, **30**, 142 (1911).

(8) Smith, *Ann.*, 289, 310 (1896); *Ber.*, **35**, 2169 (1902).



VIII

IX

Since pyrocatechol and its derivatives are very common in nature, it is perhaps of interest to point out a possible way by which they can eventually be formed from carbohydrates through furan derivatives.

At present no definitive explanation can be offered as to the mechanism of the conversion of I into III or IV. It is very probable that the reaction does not proceed according to Neber's formulas through 2-aminofuran, because by such a process the formation of a six-membered carbon-chain cannot be explained. On the other hand, it is known that the furan ring may open up even under mild experimental conditions as illustrated by the formation of levulinic aldehyde dimethylacetal[9] from 2-methylfuran in methyl alcoholic hydrogen chloride solution.

Experimental

2-Acetofuranoxime.—A solution of 2-acetofuran[10] (40 g.), hydroxylamine hydrochloride (30 g.) and anhydrous sodium acetate[11] (40 g.) in 200 cc. of ethyl alcohol was refluxed for five hours. The hot solution was filtered from the precipitated sodium chloride, the filtrate concentrated *in vacuo*, and ice water was added to the residue. The substance first separated as an oil but soon became crystalline on stirring. It was recrystallized from methyl alcohol; yield, 90%, m. p. 104°.

***p*-Toluenesulfonyl 2-Acetofuranoxime** (I).—Fifty grams of powdered *p*-toluenesulfonyl chloride was added gradually to a solution of 2-acetofuran oxime (30 g.) in 140 cc. of pyridine at −10° with stirring. After standing at 0° for two hours the reaction mixture was poured into ice water. The crystalline precipitate was filtered, washed with water, dried *in vacuo* and recrystallized from benzene by addition of petroleum ether; yield, almost quantitative, m. p. 80° with decomposition. The colorless needles were soluble in ether, benzene and acetone, sparingly soluble in alcohol, practically insoluble in water and petroleum ether.

Anal. Calcd. for $C_{13}H_{13}O_4NS$: C, 55.90; H, 4.69. Found: C, 55.95; H, 4.61.

Hexen-2-dion-4,5-diethylacetal-1 (III).—A solution of fifty grams of the *p*-toluenesulfonyl ester (I) in 250 cc. of 95% ethyl alcohol was shaken for five days at room temperature on the machine. Then the ammonium *p*-toluenesulfonate precipitate was filtered off, the filtrate was concentrated *in vacuo* at 30–35° bath-temperature to a small volume, to which 250 cc. of ether was added. After removal by filtration of a small quantity of the ammonium salt, the ether solution was stirred with a little water, dried with anhydrous sodium sulfate and the solvent distilled off first under atmospheric pressure, finally *in vacuo*. The remaining liquid distilled at 75–90° (3 mm.). The bath temperature must not rise above 130° because the resinous residue on overheating decomposes with explosion-like violence. On rectification most of the substance distilled at 65–68° (1 mm.); yield, 80%. The acetal had a yellowish-green color, it was readily soluble in water and in the common organic solvents. It reduced Fehling solution and ammoniacal silver nitrate solution in the cold. Its freshly prepared aqueous solution was neutral to litmus and did not react with Schiff reagent. On standing, the solution became acidic because of decomposition with the production of acetic acid.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.96; H, 8.06; mol wt., 200.2. Found: C, 59.64; H, 8.25; mol. wt., 198, by freezing point depression in benzene.

For the attempted preparation of an adduct from III with maleic anhydride an ether solution of the equivalent quantities of the components was kept for two days in the ice-chest. After distillation of the solvent the starting materials were recovered unchanged almost quantitatively.

Hexen-2-dion-4,5-dimethylacetal-1 (IV).—The preparation of the dimethylacetal was carried out in the same manner as that of the diethylacetal (III), but methanol was applied instead of ethanol. The resulting yellowish-green liquid showed the same chemical behavior as III; yield, 80–90%, b. p. 80.5–81.5° (3 mm.).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.78; H, 7.03; mol. wt., 172.2. Found: C, 55.93; H, 7.11; mol. wt., 171.6, by freezing point depression in benzene.

Hexan-dion-4,5-diethylacetal-1 (V).—A 20.2-g. quantity of hexen-2-dion-4,5-diethylacetal-1 (III) in 100 cc. of ethyl alcohol was hydrogenated in the presence of 3 g. of palladium–charcoal (10% Pd) at room temperature and at atmospheric pressure. The substance took up 1 mole of hydrogen during a few hours, then the rate of the reaction decreased. At this point the hydrogenation was interrupted, the filtered solution evaporated *in vacuo*, and the remaining liquid distilled at 73–75° (3 mm.); yield, 80%. The almost colorless substance reduced ammoniacal silver nitrate solution in the cold; it was readily soluble in water and in the common organic solvents. According to Zerewitinow's method the substance contained about 0.3 atom of active hydrogen.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91; mol. wt., 202.2. Found: C, 59.45; H, 9.19; mol. wt., 200.5, by freezing point depression in benzene.

Hexandion-4,5-dimethylacetal (VI).—This substance was prepared from the unsaturated dimethylacetal (IV) as V from III, b. p. 78–82° (2 mm.). Both of the saturated acetals V and VI showed very similar properties. According to Zerewitinow's method the substance contained about 0.2 atom of active hydrogen.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.14; H, 8.10. Found: C, 54.64; H, 8.21.

Hydrolysis of the Hexen-2-dion-4,5-diemthylacetal-1 (IV).—A solution of 5 g. of the acetal in 50 cc. of 2% sulfuric acid was refluxed for thirty minutes. The solution first became yellow, then brown and finally some resinous product precipitated. The filtered solution was evaporated *in vacuo*, the distillate exactly neutralized with 0.1 *N* sodium hydroxide solution, and then about two-thirds of its volume was distilled. In this distillate the presence of methyl alcohol could be demonstrated by Denigès' reaction. The residue was evaporated to dryness and mixed with a saturated silver nitrate solution. The crystalline precipitate was filtered off, washed with a little cold water and dried *in vacuo;* it proved to be silver acetate.

Anal. Calcd. for $C_2H_3O_2Ag$: Ag, 64.64. Found: Ag, 64.18.

Hexen-2-dion-4,5-aldoxime and its Benzoyl Derivative.—To 0.5 g. of either unsaturated acetal III or IV in 10 cc. of water there was added a concentrated aqueous solution of 0.5 g. of hydroxylamine hydrochloride. The oxime soon precipitated in needles which were recrystallized from hot water; m. p. 236° with decomposition. It was soluble in alkalies, sparingly soluble in cold water and alcohol, and almost insoluble in the other usual solvents. Its aqueous solution showed a red coloration with ferric chloride.

Anal. Calcd. for $C_6H_7O_3N$: C, 51.03; H, 4.96; N, 9.92. Found: C, 51.26; H, 5.18; N, 9.99.

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[9] Harries, *Ber.*, **31**, 37 (1898).

[10] Sandolin, *ibid.*, **33**, 492, 1176 (1900): Torrey and Zanetti, *Chem. Zentr.*, **82**, I, 81 (1911).

[11] Sandolin (ref. 10) applied sodium carbonate instead of sodium acetate, and the yield was only 50%.

For benzoylation 0.1 g. of the oxime, dissolved in 15 cc. of 2 *N* sodium hydroxide solution, was shaken with 0.5 g. of benzoyl chloride for fifteen minutes. The ester was filtered, washed with water and recrystallized from alcohol; colorless needles, m. p. 168°.

Anal. Calcd. for $C_{18}H_{11}O_4N$: N, 5.71. Found: N, 5.77.

bis-Phenylhydrazone of Hexen-2-dion-4,5-al-1.—One gram of the acetal III or IV, dissolved in 30 cc. of water, was mixed with a solution of 3 g. of phenylhydrazine hydrochloride in 15 cc. of water. The bis-phenylhydrazone precipitated as an oil which soon changed into crystals. It was filtered, washed with water, and recrystallized from alcohol with activated carbon; orange-red crystals, m. p. 209° with decomposition.

Anal. Calcd. for $C_{18}H_{18}ON_4$: C, 70.55; H, 5.92; N, 18.29. Found: C, 70.48; H, 5.94; N, 18.19.

Oxidation of Hexen-2-dion-4,5-dimethylacetal-1 (IV): (a) **Oxidation by Ozone.**—Into a solution of the acetal (6 g.) in anhydrous chloroform (30 cc.) 1.1 mole of ozone was introduced. Then the solvent was distilled off *in vacuo* and the oily residue was boiled with 60 cc. of water under reflux until clear solution was obtained (two hours). Addition of phenylhydrazine in acetic acid solution caused the precipitation of glyoxal-bisphenylhydrazone which was recrystallized from alcohol; m. p. and mixed m. p. with an authentic sample, 169°.

(b) **Oxidation with Potassium Permanganate.**—To 6.8 g. of IV in 50 cc. of water which was made slightly alkaline by addition of a few drops of potassium hydroxide solution, there was added at 5 to 10° 28 g. of potassium permanganate in 500 cc. of water, in small portion during twelve hours with stirring. After completed oxidation the solution, filtered from the precipitated manganese dioxide, was concentrated *in vacuo* to 100 cc., then acidified with dilute sulfuric acid to congo paper, and distilled. About 70 cc. of the distillate, after neutralization with 0.1 *N* alkali, was evaporated to dryness on the steam-bath. For decomposition of the sodium formate which formed part of the residue, the latter was treated with concentrated sulfuric acid, then diluted with water and the solution was distilled. From this distillate the acetic acid, produced by the oxidation, was isolated in form of its silver salt.

Anal. Calcd. for $C_2H_3O_2Ag$: Ag, 64.64. Found: Ag, 64.12.

From the residue of the first distillation, by addition of an acetic acid solution of phenylhydrazine, the phenylhydrazine salt of oxalic acid was obtained in colorless plates; m. p. and mixed m. p. with an authentic sample, 182°.

(c) **Oxidation with Hydrogen Peroxide.**—One g. of IV in 10 cc. of glacial acetic acid was refluxed with 10 cc. of a 15% hydrogen peroxide solution for four hours. The colorless substance, obtained after evaporation of the solution *in vacuo* and recrystallization of the solid residue from water, was identified as maleic acid; m. p. and mixed m. p. with an authentic sample, 132°.

Oxidation of Hexandion-4,5-dimethylacetal-1 (VI) with Silver Oxide.—Four grams of the saturated acetal (VI) in 100 cc. of water was refluxed for one hour with 4 g. of freshly prepared silver oxide. The hot, filtered solution was then saturated with hydrogen sulfide, filtered from the precipitated silver sulfide and evaporated to dryness on the steam-bath. The solid residue was recrystallized from absolute alcohol. The colorless substance proved to be succinic acid; m. p. and mixed m. p. with an authentic sample, 183°.

1-Phenyl-3-acetodihydropyridazine Phenylhydrazone (VII).—About 0.5 g. of the saturated acetal V or VI was heated on the steam-bath for ten minutes with 1 g. of phenylhydrazine in 5 cc. of glacial acetic acid. After the precipitate was filtered and washed with water and alcohol, it had the appearance of a pale-yellow crystalline powder, which was practically insoluble in water and the other usual solvents. The substance did not melt up to 280°.

Anal. Calcd. for $C_{18}H_{18}N$: C, 74.41; H, 6.24; N, 19.34. Found: C, 74.51; H, 6.44; N, 19.12.

Formation of Pyrocatechol on Hydrolysis of Hexandion-4,5-dimethylacetal-1 (VI).—A solution of the acetal (2.5 g.) in 2% sulfuric acid (60 cc.) was refluxed for one hour. After cooling the faintly brown solution was saturated with sodium bicarbonate and extracted with ether. The ether extract was dried with anhydrous sodium sulfate, evaporated, and the residue distilled *in vacuo;* b. p. 111–112° (3 mm.). The distillate crystallized from ligroin in colorless plates which showed all the characteristic properties of pyrocatechol; m. p. and mixed m. p. with authentic sample, 104°. The aqueous solution of the substance gave an emerald-green coloration with ferric chloride.

Anal. Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.45. Found: C, 65.78; H, 5.59.

Summary

On shaking *p*-toluenesulfonyl 2-acetofuranoxime (I) with ethanol or methanol, not the expected 2-aminofuran was formed, but unsaturated aliphatic compounds, represented by the formulas $C_{10}H_{16}O_4$ (III) and $C_8H_{12}O_4$ (IV), respectively. The constitution and configuration of these substances were determined by various methods which definitely established their identities as being *cis*-hexen-2-dion-4,5-diethylacetal-1 and -dimethylacetal-1, respectively.

The corresponding aldehydes could not be produced because the carbon-chain between the carbonyl groups 4 and 5 split up with formation of acetic acid, even in cold aqueous solution.

The hydrolysis of the saturated acetals also led to a surprising result; because instead of the expected hexandion-4,5-al-1, there was obtained pyrocatechol.

It is suggested that natural pyrocatechol derivatives might be formed in a similar manner from carbohydrates through furan derivatives.

Cluj-Kolozsvár, Rumania Received January 31, 1947