The Base-catalyzed Condensation of Nitrophenylpyruvates. I. α-Oxo-β-(o-nitrophenyl)-γ-(o-nitrobenzyl)-γ-ethoxycarbonyl-γ-butyrolactone

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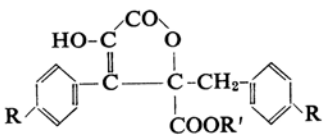
(Received February 11, 1964)

In connection with our synthetic study of the amino acid metabolism, we wished to prepare a quantity of ethyl *o*-nitrophenylpyruvate. The ester had been studied extensively by Wislicenus and Thoma,[1] who prepared it by the condensation of *o*-nitrotoluene with ethyl oxalate in the presence of potassium ethoxide in dry ether.

We attempted, however, to prepare the ester more economically by modifying the DiCarlo method[2] for the acid. *o*-Nitrotoluene was condensed with ethyl oxalate in the presence of sodium ethoxide in boiling ethanol. The reaction mixture was saturated with hydrogen chloride. From a benzene solution of the reaction product, the keto ester was isolated as a bisulfite adduct. When the adduct was decomposed with mineral acid, a crystalline substance, $C_{20}H_{26}O_9N_2$, insoluble in benzene was obtained. This compound usually appeared as needles decomposing at 180°C; however, it was occasionally obtained as rhombi decomposing at 183.5°C. Most of the reactions were carried out with the former.

A comparison of the composition of this compound with that of ethyl *o*-nitrophenylpyruvate indicated that the compound had been formed by the condensation of two moles of the pyruvate with a loss of one mole of ethanol. The enolate anion from the starting ester might attack another mole of the ester, either at the ester carbonyl or at the keto carbonyl, to form a triketo ester I or a ketolactone ester II respectively.

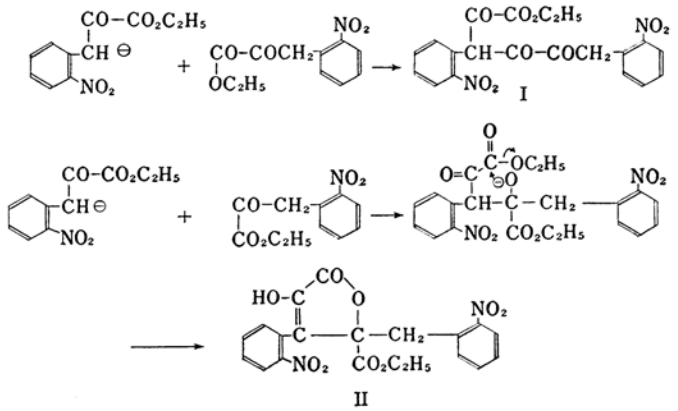
Hemmerlé[3] has found the self-condensation products of phenylpyruvic esters to be α-oxo-β-phenyl-γ-benzyl-γ-alkoxycarbonyl-γ-butyrolactone (III, R=H). Cagniant[4] obtained analogous compounds III (R=NO_2 and CH_3O, R′=H) from *p*-nitro- and *p*-methoxyphenylpyruvic acids.



III

Similarly, the compound obtained here also may probably be expressed by the structure II. This will be established by the following chemical evidence.

The compound II is weakly acidic and soluble in aqueous alkali. The acetylation of II with acetic anhydride gave a monoacetate IV, and treatment with diazomethane yielded



II

1) W. Wislicenus and E. Thoma, *Ann.*, **436**, 42 (1924).
2) F. T. DiCarlo, *J. Am. Chem. Soc.*, **66**, 1420 (1944).
3) R. Hemmerlé, *Ann. chim.*, [9] **7**, 226 (1917).
4) Mme. P. Cagniant, ibid., **7**, 442, 457, 470 (1952).

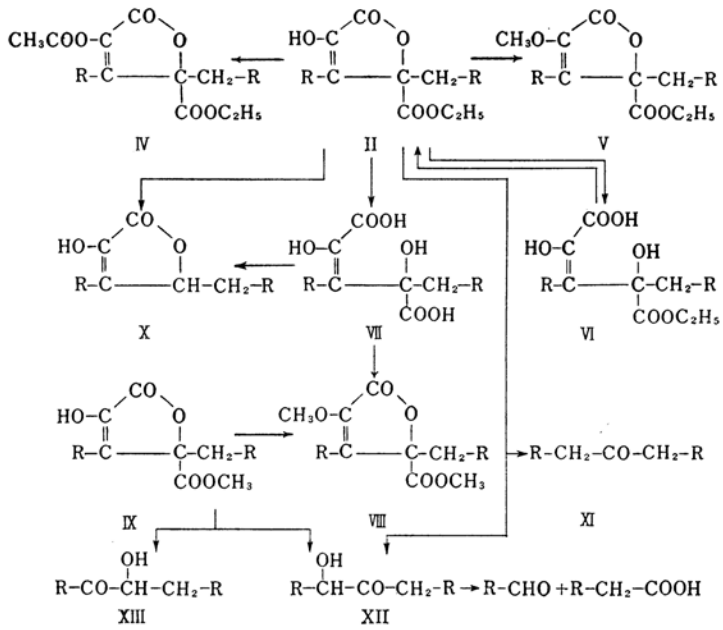


Chart 1.

a monomethyl ether V. They were no longer acidic.

The hydrolysis of II with aqueous sodium hydroxide at room temperature for one and a half hours gave a pale green acid, VI, melting at ca. 95°C.[5] The methylation of the acid VI with diazomethane gave the methyl ether V, while esterification with ethanolic hydrogen chloride formed the original ester II.

In contrast to the above hydrolysis, the hydrolysis of II with aqueous sodium hydroxide at room temperature for 22 hr. gave an acid, VII, decomposing at 144.5~145°C. This acid, on treatment with diazomethane, was changed to a methyl ether VIII (m. p. 169.5~170.5°C), whose composition, $C_{20}H_{16}O_9N_2$, was less by CH_2 than that of the ethyl ester V. The methyl ether VIII was identified with the enol methyl ether of the methyl ester IX which was prepared by the condensation of *o*-nitrotoluene with methyl oxalate under the same conditions as used for the ethyl ester II.

The attempted esterification of the acid VII with ethanolic hydrogen chloride gave a lactone X (m. p. 191~191.5°C), the structure of which was determined on the basis of its composition, $C_{17}H_{14}O_7N_2$, and its infrared spectrum (see Experimental). This compound was still weakly acidic, as was to be expected from its structure, and gave a methyl ether with diazomethane. The hydrolysis of II with a mixture of hydrochloric and acetic acids gave the same compound X; however, the hydrolysis was very hard.

The oxidation of II or IX with alkaline hydrogen peroxide gave various results, as did the alkaline hydrolysis.[5] Three neutral products were isolated. One of them, a ketone XI, $C_{15}H_{12}O_5N_2$, was identified with the 1,3-bis(*o*-nitrophenyl)-2-propanone prepared by the nitration of dibenzyl ketone. The positions of the nitro groups in the synthetic sample were confirmed by permanganate oxidation to *o*-nitrobenzoic acid. The second product, XII ($C_{15}H_{12}O_6N_2$; m. p. 142~143°C), gave a positive Fehling reaction indicative of a ketol function. This compound was assumed to possess the structure XII from the fact that the Treibs oxidation of this compound yielded *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid. The third product, XIII (m. p. 95°C), was isomeric with the ketol XII and was tentatively assigned the structure of 1,3-bis(*o*-nitrophenyl)-2-propanol-1-one from its infrared spectrum (see Experimental); however, it gave a negative Fehling reaction.

Jarrousse[6] has noted that the α-ketol analogous to XIII obtained by the decarboxylation of an acid that had been obtained by the permanganate oxidation of di-(phenylpyruvic acid) is isomerized readily to the α-ketol corresponding to XII. The fact that no such

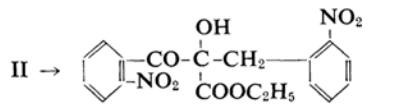
5) The product was erratic, varying in response to slight differences in the reaction conditions, and so was hard to purify.

6) J. Jarrousse, *Ann. chim.*, 9, 157 (1938).

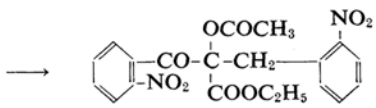
isomerization was observed with the compound XIII made the postulated structure doubtful.

The above transformations of the compound II are summerized in Chart 1.

The permanganate oxidation of II in acetone gave a hydroxy ester XIV (m. p. 131.5~132°C), together with *o*-nitrobenzoic and oxalic acids. This compound gave a negative ferric chloride reaction; its structure was postulated from the composition, $C_{18}H_{18}O_8N_2$, and its infrared spectrum (see Experimental). The acetylation of XIV with acetic anhydride gave an acetate, XV. The acetate was so stable that it was sublimed without decomposition on attempted pyrolysis under reduced pressure.[7]



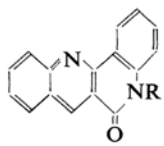
XIV



XV

The hydrolysis of XIV with hydrochloric acid gave *o*-nitrophenylacetic acid in a 69% yield. The mechanism of the unexpected formation of this acid has not been clarified.

The hydrogenation of XIV in the presence of palladium-on-carbon gave yellow crystals melting at 354°C. This compound exhibited an ultraviolet spectrum completely identical with that of 5-methylquino[4, 3-b]quinoline-6(5*H*)-one[8] (XVII) and was assigned the structure of the quinoquinolone XVI.



XVI: R=H
XVII: R=CH_3

Experimental[9]

α-Oxo-β-(*o*-nitrophenyl)-γ(*o*-nitrobenzyl)-γ-ethoxycarbonyl-γ-butyrolactone (II).—Into a sodium ethoxide solution prepared from 23 g. of sodium and 270 cc. of ethanol was added a mixture of 137 g. of *o*-nitrotoluene and 146 g. of diethyl oxalate in one portion with stirring at room temperature. The resulting deep-red mixture was heated while continuously being stirred at 125°C for half an hour. After cooling, the mixture was acidified by bubbling dry hydrogen chloride. The precipitated sodium chloride was filtered off, and the filtrate was concentrated. The residue as a benzene solution was treated with aqueous sodium bisulfite (360 g. in 600 cc. of water) to form a quantity of precipitates. The precipitates were filtered, washed with benzene, and decomposed by treatment with diluted sulfuric acid (90 cc. in 350 cc. of water) and 250 cc. of benzene at 50~60°C for one hour. The insoluble material was then filtered from the cooled mixture (43.8 g.). The benzene layer of the filtrate was diluted with ether and then extracted with 10% aqueous sodium carbonate. The acidification of the extract gave an additional 6.4 g. of the precipitates, which were combined with the above-mentioned insoluble material (total 50.2 g., 23%) and twice recrystallized from ethanol to yield pure ester II as a powder, decomposing at 182~182.5°C. ν_{max} 3330 (OH), 1773, 1698 (C=O or C=C), 1529, 1348, 1335 cm^{-1} (NO_2). (Found: C, 56.07; H, 3.74; N, 6.45. Calcd. for $C_{20}H_{16}O_9N_2$: C, 56.08; H, 3.77; N, 6.54%.) Allowing the mother liquor of recrystallization to evaporate gave a mixture of needles and rhombi; these two forms of crystals were separated by hand. Since the needles (Found: C, 56.21; H, 3.94%), decomposing at 183.5°C, showed the same infrared spectrum as the ester in powder, the ester in powder was assumed to be mainly composed of this form. The rhombi decomposed at 183.5°C (Found: C, 56.18; H, 4.01%). ν_{max} 3330 (OH), 1748 (C=O), 1695 (C=C), 1522, 1355 cm^{-1} (NO_2).

Monoacetate IV.—Heating 0.5 g. of II with acetic anhydride for five hours at 100°C gave 0.5 g. of IV, which, after recrystallization from acetic acid, melted at 170.5~171°C (Found: C, 56.49; H, 3.95; N, 5.97. Calcd. for $C_{22}H_{18}O_{10}N_2$: C, 56.17; H, 3.86; N, 5.96%).

Monomethyl Ether V.—A solution of 1 g. of II in aqueous potassium hydroxide (0.39 g. in 8 cc. of water) was treated with 0.9 g. of dimethyl sulfate to give a yellow oil which solidified in a short time. Extraction with benzene, followed by washing with aqueous sodium carbonate and the evaporation of the solvent, gave yellow plates, which, after three recrystallizations from benzene, melted at 140.5~141.5°C (Found: C, 57.12; H, 4.09; N, 6.53; mol. wt. (Rast): 406. Calcd. for $C_{21}H_{18}O_9N_2$: C, 57.01; H, 4.10; N, 6.33%; mol. wt. 442).

The methylation of 1 g. of II in methanol with diazomethane gave 0.9 g. of the methyl ether V melting at 137~138.5°C. Recrystallization from benzene gave 0.73 g. of a pure material which melted at 137.5~138.5°C. Mixed melting point determination with the above methyl ether did not show any depression.[10]

The Alkaline Hydrolysis of II. — *Carboxylic Acid VI.* — A solution of II (2 g.) in 23 cc. of N aqueous sodium hydroxide was allowed to stand

7) Steric circumstances might hinder the formation of a six-membered-ring transition state favorable for pyrolysis.

8) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1955, 381.

9) All melting points are uncorrected. The infrared spectra were measured in Nujol mull and are expressed in ν_{max} cm^{-1}. The authors are much indebted to Mr. Jun'ichi Gōda and his associates for their elementary analyses and to Mrs. Michino Butsugan and Miss Hiromi Tokuda for their infrared spectral measurements.

10) The discrepancy between the melting points is due to the use of different thermometers.

for half an hour at room temperature. Acidification with N hydrochloric acid precipitated a pale-green acid, which, after recrystallization from acetic acid-ligroin, decomposed at 95°C, solidified at 100°C, and then decomposed at 159~165°C again. ν_{max} 3300 (OH), 1786, 1695 (C=O).

Carboxylic Acid VII.—Allowing a solution of II in 20 cc. of 2 N sodium hydroxide to stand for 22 hr. at room temperature gave an acid VII, which, after three recrystallizations from acetic acid-ligroin, decomposed at 152.5°C. (Found: C, 52.64; H, 3.04; N, 6.80. Calcd. for $C_{18}H_{14}O_{10}N_2$: C, 51.68; H, 3.37; N, 6.70%).

The Attempted Esterification of the Acid VI with Ethanolic Hydrogen Chloride.—Into a solution of 200 mg. of acid VI in 5 cc. of dry ethanol hydrogen chloride was bubbled for half an hour, and then the mixture was refluxed for 40 min. After the removal of the solvent, the residue was dissolved in ether, washed with aqueous sodium bicarbonate and water successively, and dried. The distillation of the ether left a colorless powder, decomposing at 182~183°C, in a quantitative yield. It was identified with II by admixture test and infrared comparison.

The Methylation of the Acid VI with Diazomethane.—The methylation of VI with methanolic diazomethane afforded a neutral compound melting at 146.5~147°C, which was identified with the methyl ether V by mixed melting determination and infrared comparison.

The Attempted Esterification of the Acid VII with Ethanolic Hydrogen Chloride. — *α-Oxo-β-(o-nitrophenyl)-γ-(o-nitrobenzyl)-γ-butyrolactone (X).* — A suspension of 0.14 g. of VII in 4 cc. of dry ethanol was refluxed for 30 min. while hydrogen chloride was being introduced. Rubbing the neutral fraction with benzene-ethanol gave 88 mg. of crystals, which, after recrystallization from ethanol, melted at 187~189°C. ν_{max} 3300 (OH), 1745 (C=O), 1695 cm^{-1} (C=C).

Found: C, 57.59; H, 3.36; N, 7.64. Calcd. for $C_{17}H_{12}O_7N_2$: C, 57.31; H, 3.40; N, 7.86%.

α-Oxo-β-(o-nitrophenyl)-γ-(o-nitrobenzyl)-γ-methoxycarbonyl-γ-butyrolactone (IX). — Into a sodium methoxide solution prepared from 11.5 g. of sodium and 94 cc. of methanol, 59 g. of dimethyl oxalate and then 68.5 g. of *o*-nitrotoluene were added. The mixture was refluxed vigorously for 20 min. and acidified by the introduction of dry hydrogen chloride. After the removal of salt by filtration and that of the solvent by evaporation, the residue was treated with ice and benzene to separate a yellow, insoluble material. The benzene layer, after filtration, was extracted with three portions of 10% aqueous sodium carbonate, and the extract was acidified with 2 N hydrochloric acid to give reddish brown precipitates, which were combined with the above-obtained, insoluble material and recrystallized from ethanol to yield colorless crystals decomposing at 185~186°C. (Found: C, 55.31; H, 3.62; N, 7.03. Calcd. for $C_{19}H_{14}O_9N_2$: C, 55.07; H, 3.38; N, 6.76%.)

α-Methoxy-β-(o-nitrophenyl)-γ-(o-nitrobenzyl)-γ-methoxycarbonyl-$\Delta^{\alpha,\beta}$-butenolide (VIII).—*The Methylation of the Acid VII with Diazomethane.*—The methylation of VII with diazomethane in methanol gave a methyl ether melting at 169.5~170.5°C. (Found: C, 56.29; H, 4.03; N, 6.83. Calcd. for $C_{20}H_{16}O_9N_2$: C, 56.08; H, 3.77; N, 6.54%.) This methyl ether was identified with the methyl ether VIII synthesized below by the admixture test and by an infrared spectral comparison.

The Methylation of Compound IX.—The methylation of IX with methanolic diazomethane gave a methyl ether which, after recrystallization from benzene, melted at 167°C.

The Oxidation of Compound II or IX with Alkaline Hydrogen Peroxide.—*The Formation of 1,3-Bis(o-nitrophenyl)-2-propanone.*—A solution of 2 g. of II in 20 cc. of N sodium hydroxide was treated with 40 cc. of 30% hydrogen peroxide. An exothermic reaction occurred. The mixture was allowed to stand overnight, and was then acidified and extracted with ether. The ether extract, after being washed with aqueous sodium bicarbonate, gave yellow crystals, which, after recrystallization from ethanol, melted at 136~137°C. This material was identified with the specimen synthesized below by the admixture test and by a comparison of the infrared spectra.

The Formation of Compound XII.—A solution of 1 g. of II in 5 cc. of N sodium hydroxide was left to stand with 20 cc. of 30% hydrogen peroxide for two days. Within one hour the mixture became cloudy. After extraction with ether, an additional amount of N sodium hydroxide was added to the aqueous layer to cause an exothermic reaction. The mixture was then allowed to stand overnight and extracted with ether. The combined ether extracts were shaken with aqueous sodium bicarbonate. The aqueous layer was acidified with hydrochloric acid and extracted with ether again. The extract, after the removal of the solvent, left a yellow oil, which solidified and was repeatedly recrystallized from ethanol to give the ketol XII, melting at 142~143°C. This compound reduced the Fehling solution. ν_{max} 3480 (OH), 1727 cm^{-1} (C=O). (Found: C, 57.44; H, 3.93; N, 8.64. Calcd. for $C_{15}H_{12}O_6N_2$: C, 56.96; H, 3.82; N, 8.86%.)

The Formation of Compound XIII.—A solution of 3 g. of compound IX in 60 cc. of N sodium hydroxide was allowed to stand for 50 min. and then treated with 2 cc. of 30% hydrogen peroxide. The mixture was left overnight and then acidified to give 2.39 g. of precipitates decomposing at 151~159°C. The precipitates were dissolved in 12 cc. of N sodium hydroxide and treated with 48 cc. of hydrogen peroxide. After the mixture had been left to stand overnight, it was acidified to give precipitates, which afforded 0.81 g. of an acid fraction and 0.98 g. of neutral fraction. The acid fraction was treated with hot benzene. The benzene-soluble acid (0.21 g.) melted at 131~134°C and was identified with *o*-nitrophenylacetic acid. The benzene-insoluble fraction was methylated with diazomethane to give a compound melting at 166°C, which was identified with the methyl ether VIII. The neutral fraction was recrystallized from benzene to give 0.25 g. of a compound melting at 138~141°C, which was found to be identical with the compound XII obtained above. From the mother

liquor of the recrystallization compound XIII (m. p. 95°C) was obtained. This compound did not reduce the Fehling solution. ν_{max} 3380 (OH), 1705 cm^{-1} (C=O).

Found: C, 57.34; H, 3.93; N, 8.34. Calcd. for $C_{15}H_{12}O_6N_2$: C, 56.96; H, 3.82; N, 8.86%.

1, 3-Bis(*o*-nitrophenyl)-2-propanone.—Into 4 g. of fuming nitric acid (d=1.53) was added a mixture of 2 g. of dibenzyl ketone and 4 g. of acetic anhydride at −3∼−5°C with stirring. After 40 min. the mixture was poured onto ice, and the resulting oil was extracted with benzene. The benzene extract was washed successively with aqueous sodium bicarbonate and water, followed by drying and chromatography on active alumina. The first fraction eluted with benzene yielded colorless plates (450 mg.), which, after recrystallization from ethanol, melted at 141∼141.5°C. (Found: C, 60.23; H, 4.06; N, 9.31. Calcd. for $C_{15}H_{12}O_5N_2$: C, 60.00; H, 4.00; N, 9.33%.) This compound, on oxidation with potassium permanganate in aqueous alkali, produced *o*-nitrobenzoic acid (m. p. 147°C).

The Treibs Oxidation of Compound XII.—Into a warm solution of XII in 2 cc. each of methanol and ethanol was added one drop of a vanadium pentoxide solution, prepared from 100 mg. of vanadium pentoxide and 5 cc. of 30% hydrogen peroxide, and then 0.8 cc. of 30% hydrogen peroxide in three portions; white precipitates were thus produced. After the addition of a sufficient amount of acetone to make a clear solution, the solution was left to stand for three days. The solvent was distilled off and the residue, after the addition of water, was extracted with benzene-ether. The acid fraction gave an acid melting at 137.5∼138°C, which was identified with *o*-nitrophenylacetic acid by mixed melting point determination. The neutral fraction was converted to a 2, 4-dinitrophenylhydrazone decomposing at 235∼250°C, which was identified with that of *o*-nitrobenzaldehyde, decomposing at 250°C, by infrared comparison.

The Permanganate Oxidation of Compound II.—Into a solution of 2.57 g. of II in 400 cc. of acetone 2.53 g. of potassium permanganate was added in one portion, and then the mixture was stirred for 7 hr. at room temperature. The acetone solution, after the filtration of manganese dioxide and the distillation of the solvent, gave 1.66 g. of a residue, which, after recrystallization from benzene-ligroin, melted at 131.5∼132°C. ν_{max} 3485 (OH), 1730 (shoulder), 1712 cm^{-1} (C=O). (Found: C, 55.87; H, 4.30; N, 7.21. Calcd. for $C_{18}H_{16}O_8N_2$: C, 55.67; H, 4.15; N, 7.21%.)

Acetate XV.—A mixture of 0.5 g. of XIV and 5 cc. of acetic anhydride was heated for one hour in the presence of one drop of concentrated sulfuric acid to give a crude acetate in a quantitative yield. Two recrystallizations from ethanol provided the pure acetate melting at 129°C. ν_{max} 1745, 1705 cm^{-1} (C=O) (Found: C, 56.33; H, 4.38; N, 6.70; mol. wt. (Rast), 423. Calcd. for $C_{20}H_{18}O_9N_2$: C, 55.81; H, 4.22; N, 6.51%; mol. wt., 430).

The Hydrolysis of XIV.—A mixture of 400 mg. of XIV, 100 cc. of 2 N hydrochloric acid and 30 cc. of acetic acid was boiled under reflux for 18 hr. The acid fraction gave 100 mg. of *o*-nitrophenylacetic acid (m. p. 136.5°C). The neutral fraction gave 88 mg. of the recovered XIV.

The Hydrogenation of XIV.—A solution of 200 mg. of XIV in 40 cc. of acetic acid was hydrogenated in the presence of 40 mg. of palladium-on-carbon under ordinary pressure. Six molar equivalents of hydrogen were absorbed in 5 hr., 20 min. After the catalyst had been removed, the solvent was distilled under reduced pressure to give 170 mg. of a yellow powder, which, after recrystallization from acetic acid, decomposed at 354°C. The analytical sample was purified by sublimation at 270°C/10 mmHg. ν_{max} 3175 (NH), 1667 cm^{-1} (C=O). λ_{max}^{EtOH} mμ (log ε): 227 (4.54), 233 (4.52), 274 (4.82), 290 (4.36), 362 (3.66). (Found: C, 77.68; H, 4.33; N, 12.34. Calcd. for $C_{16}H_{10}ON_2$: C, 78.03; H, 4.09; N, 11.38%.)

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