

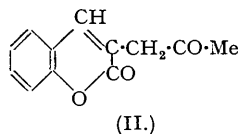
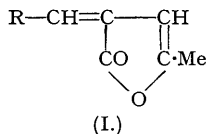
NOTES.

The Production of Coumarin Derivatives by Condensation of o-Hydroxy-aldehydes with $\Delta^{\beta\gamma}$ -Angelicalactone.

By D. H. MARRIAN and P. B. RUSSELL.

THIELE, TISCHBEIN, and LÖSSOW (*Annalen*, 1901, **319**, 185) condensed $\Delta^{\beta\gamma}$ -angelicalactone with benzaldehyde and anisaldehyde in presence of diethylamine and showed that under these conditions benzaldehyde yielded α -benzylidene-laevalic acid cyclised by heating with acetic anhydride and a little sulphuric acid to γ -methyl- α -benzylidene- $\Delta^{\beta\gamma}$ -butenolide (I; R = Ph); anisaldehyde yielded the corresponding α -anisylidene lactone (I; R = *p*-MeO·C₆H₄) directly. More recently von Oettingen (*J. Amer. Chem. Soc.*, 1930, **52**, 2024) condensed a series of aldehydes including salicyl-

aldehyde and β -resorcylaldehyde under similar conditions with $\Delta^{\beta\gamma}$ -angelicalactone and obtained products to which he ascribed structures of type (I).



In the course of other investigations in this laboratory we had occasion to condense a series of aromatic aldehydes with $\Delta^{\beta\gamma}$ -angelicalactone. We observed that the products from *o*-hydroxy-aldehydes differed considerably in their properties from the others. They gave analytical values in agreement with those expected for structure (I), but were almost colourless and, as had been observed by von Oettingen (*J. Pharm.*, 1930, **39**, 59), were unexpectedly soluble in water. Moreover, they were ketonic and gave semicarbazones and 2 : 4-dinitrophenylhydrazones under normal conditions; compounds such as (I; R = *p*-MeO-C₆H₄) failed to react with ketone reagents under similar conditions.

When refluxed with methanolic potassium hydroxide, the condensation product of salicylaldehyde and $\Delta^{\beta\gamma}$ -angelicalactone gave a deep yellow solution from which by acidification the original substance could be recovered unchanged; Thiele, Tischbein, and Lössow (*loc. cit.*) showed that (I; R = *p*-MeO-C₆H₄) gave on similar treatment α -anisylidene-laevalic acid. The condensation product gave a positive iodoform reaction and on oxidation with dichromate gave coumarin-3-carboxylic acid. We therefore conclude that the condensation product is, in fact, 3-acetonilycoumarin (II). In the same way, the condensation of $\Delta^{\beta\gamma}$ -angelicalactone with β -resorcylaldehyde gives 7-hydroxy-3-acetonilycoumarin and with 2-hydroxy-1-naphthaldehyde 3-acetonily-5 : 6-benzocoumarin. Formation of coumarin derivatives by this means is presumably a general property of *o*-hydroxy-aldehydes. These findings incidentally vitiate certain conclusions drawn by von Oettingen (*J. Pharm.*, *loc. cit.*) as to the relationship between anthelmintic properties and chemical constitution of the products from salicylaldehyde and β -resorcylaldehyde.

3-Acetonilycoumarin.—Salicylaldehyde (6.1 g.) condensed with $\Delta^{\beta\gamma}$ -angelicalactone (4.9 g.) in presence of triethylamine (20 drops) gave colourless needles of 3-acetonilycoumarin, m. p. 97—98°; von Oettingen (*J. Amer. Chem. Soc.*, *loc. cit.*) gives m. p. 96° for " α -salicylal- Δ_2 -angelica lactone" (Found : C, 71.0; H, 5.0. C₁₂H₁₀O₃ requires C, 71.3; H, 4.9%). The product gave a semicarbazone separating from glycol monomethyl ether in colourless prisms, m. p. 234—235° (decomp.) (Found : N, 15.8. C₁₃H₁₃O₃N₃ requires N, 16.2%). The 2 : 4-dinitrophenylhydrazone, dark red needles from glycol monomethyl ether, had m. p. 199.5—200.5° (Found : N, 14.5. C₁₈H₁₄O₈N₄ requires N, 14.6%).

The above product (0.5 g.) was dissolved in acetic acid (5 c.c.), aqueous potassium dichromate (0.857 g. in 10 c.c.) acidified with sulphuric acid added, and the mixture left overnight then warmed on the steam-bath for 30 mins. The resulting solution was diluted with water (50 c.c.) and concentrated under reduced pressure to remove most of the acetic acid. The colourless crystalline solid which separated had m. p. 189—190° undepressed in admixture with coumarin-3-carboxylic acid (m. p. 189—191°) prepared according to Knoevenagel (*Ber.*, 1898, **31**, 2619) (Found : C, 63.5; H, 3.4. Calc. for C₁₀H₆O₄ : C, 63.2; H, 3.1%).

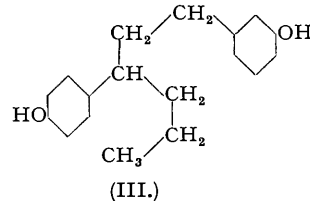
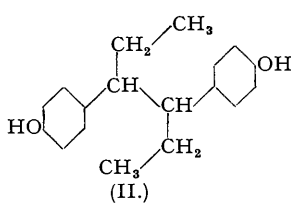
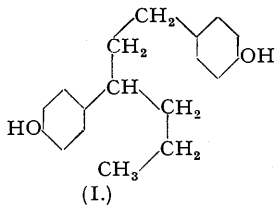
7-Hydroxy-3-acetonilycoumarin.—The condensation of β -resorcylaldehyde with $\Delta^{\beta\gamma}$ -angelicalactone gave as described by von Oettingen (*J. Amer. Chem. Soc.*, *loc. cit.*) colourless plates, m. p. 167—168°. The product yielded a colourless semicarbazone, m. p. 245—246° (decomp.) (Found : N, 15.4. C₁₃H₁₃O₄N₃ requires N, 15.3%), and an orange 2 : 4-dinitrophenylhydrazone, m. p. 253—254° (Found : N, 13.8. C₁₈H₁₄O₇N₄ requires N, 14.1%).

3-Acetonily-5 : 6-benzocoumarin.—Triethylamine (5 drops) was added to a mixture of 2-hydroxy-1-naphthaldehyde (1.7 g.) and $\Delta^{\beta\gamma}$ -angelicalactone (0.98 g.); heat was evolved and water separated at once. After having been warmed for a few minutes the whole mass set solid and was recrystallised from benzene giving the compound in faintly yellowish plates, m. p. 167°, which dissolved in methanol with a blue fluorescence and gave no coloration with ferric chloride (Found : C, 76.0; H, 5.1. C₁₆H₁₂O₃ requires C, 76.2; H, 4.7%). The substance yielded a semicarbazone crystallising from aqueous pyridine in colourless needles, m. p. 232° (decomp.) (Found : N, 13.4. C₁₇H₁₅O₃N₃ requires N, 13.6%), and a 2 : 4-dinitrophenylhydrazone forming orange needles, m. p. 188—189°, from aqueous acetic acid (Found : N, 13.3. C₂₂H₁₆O₈N₄ requires N, 13.0%).

The authors wish to thank Professor A. R. Todd, F.R.S., for his interest in this work and to express their indebtedness to the Agricultural Research Council for research grants.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [Received, December 20th, 1945.]

1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane and 1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexene.
By B. J. F. HUDSON.

In the course of recent investigations of a number of substituted 1 : 3-di-(*p*-hydroxyphenyl)propanes Stuart and Tallman (*J. Amer. Chem. Soc.*, 1943, **65**, 1579) have prepared 1 : 3-di-(*p*-hydroxyphenyl)hexane (I) and shown it to possess oestrogenic activity of a low order.



This compound (I) as distinct from others described by these authors is of interest in that it closely resembles hexoestrol (II) in structure. It was therefore considered to be worth preparing the new compound (III), which has an even closer structural similarity to hexoestrol, with a view to testing it for oestrogenic activity.

p-Methoxyacetophenone condensed with *m*-methoxybenzaldehyde to yield *m*-methoxybenzylidene-*p*-methoxyacetophenone which on hydrogenation afforded 1-(*p*-methoxyphenyl)-3-(*m*-methoxyphenyl)propan-1-one. This ketone was treated with *n*-propylmagnesium iodide, and the product dehydrated to form a substituted hexene, which on demethylation with methylmagnesium iodide gave 1-(*m*-hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexene (IV). The position of the double bond in these last two compounds is uncertain. On hydrogenation the methyl ether of (IV) gave an oily reduction product from which 1-(*m*-hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane (III) was obtained in crystalline form by demethylation.

Biological assay of compounds (III) and (IV) was carried out by Mr. A. F. Green of the Wellcome Physiological Research Laboratories, Beckenham. They were shown by the uterine weight method in rats to have less than one-thousandth of the activity of stilboestrol.

m-Methoxybenzylidene-*p*-methoxyacetophenone.—A mixture of *m*-methoxybenzaldehyde (34.1 g.) and *p*-methoxyacetophenone (37.6 g.) was treated cautiously with a solution of sodium (0.75 g.) in methanol (75 c.c.). After 24 hours the crystalline precipitate was collected, washed with methanol and water, and dried. 49.2 G. of material, m. p. 91—96°, were obtained. On recrystallisation the pure *product* separated from methanol in clusters of minute pale yellow leaflets, m. p. 96—97° (Found: C, 75.7; H, 6.5. $C_{17}H_{18}O_3$ requires C, 76.1; H, 6.0%).

1-(*p*-Methoxyphenyl)-3-(*m*-methoxyphenyl)propan-1-one.—The substituted chalcone (49 g.) was hydrogenated in ethyl acetate solution (240 c.c.) in the presence of Adams's platinum oxide catalyst (0.5 g.) at two atmospheres. After the completion of absorption of hydrogen, the catalyst was separated and the filtrate evaporated. The residual *oil* crystallised from chilled methanol in stout needles, m. p. 49—51° (Found: C, 75.8; H, 7.1. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%).

1-(*m*-Methoxyphenyl)-3-(*p*-methoxyphenyl)- Δ^3 (and/or Δ^2)-hexene.—The foregoing ketone (21.6 g.) was added slowly to the Grignard reagent prepared from magnesium (2.16 g.) and *n*-propyl iodide (17 g.) in dry ether (150 c.c.). After 12 hours the reaction mixture was worked up in the usual manner and an oily carbinol, presumably 1-(*m*-methoxyphenyl)-3-(*p*-methoxyphenyl)hexan-1-ol, obtained.

This material was dehydrated by the action of a saturated solution of hydrogen chloride in acetic acid (80 c.c.) in the course of 48 hours. The product, on distillation in a vacuum, was a colourless mobile oil (18.0 g.), b. p. 204—208°/3—4 mm.

1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)- Δ^3 (and/or Δ^2)-hexene (IV).—The oily methyl ether (7.4 g.) was mixed with a Grignard reagent prepared from magnesium (1.43 g.) and methyl iodide (9 g.) in dry ether (50 c.c.). The ether was distilled off, and the residue cautiously heated up to 175° for one hour, by which time frothing had ceased and a brittle melt had formed. This was decomposed with ice and dilute sulphuric acid, and the oily phenol extracted with ether. The *product* was a hard "glass" (4.9 g.), b. p. 250°/5 mm. (Found: C, 79.9; H, 7.4. $C_{15}H_{20}O_2$ requires C, 80.55; H, 7.5%).

1-(*m*-Methoxyphenyl)-3-(*p*-methoxyphenyl)hexane.—The oily unsaturated methyl ether (above) (10.0 g.) was hydrogenated in acetone (25 c.c.) solution in the presence of palladised charcoal (4.0 g.). After separation of the catalyst the solution was evaporated and the residual oil distilled in a vacuum. There were obtained 8.8 g., b. p. 200—201°/2 mm., of a colourless mobile oil.

1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane (III).—The above methyl ether (9.0 g.) was demethylated by heating under reflux for one hour with acetic acid (72 c.c.) and hydriodic acid (*d* 1.7, 36 c.c.). The product was worked up in the usual manner and afforded a light orange "glass," b. p. 250—260°/10 mm. After nine months this *substance* almost completely solidified. It was recrystallised from carbon tetrachloride, and separated in soft white leaflets, m. p. 80—82° (Found: C, 79.6; H, 8.2. $C_{16}H_{22}O_2$ requires C, 80.0; H, 8.2%).

All m. p.'s are uncorrected.

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Ethyl Ketoglutaconate. By J. W. CORNFORTH and R. H. CORNFORTH.

This substance, $CO_2Et \cdot CH_2 \cdot CH \cdot CO \cdot CO_2Et$, has been obtained in poor yield by oxidation of ethyl glutaconate with selenium dioxide. Its ultra-violet absorption has been measured.

A mixture of ethyl glutaconate (12 g.), selenium dioxide (7 g.), and acetic acid (60 c.c.) was boiled under reflux for 45 minutes, the selenium removed, and the solvent evaporated under low pressure. After being washed in ether with sodium bicarbonate solution the product was distilled, giving 3 g., b. p. ca. 100°/1 mm. This was redistilled and collected up to 95°/0.1 mm.; the distillate was treated with sodium bisulphite solution (5 c.c.; saturated). After a few minutes the crystalline adduct was collected, washed with ether, and decomposed by cautious brief warming with dilute sulphuric acid. The oil was isolated in the usual manner and distilled, giving *ethyl ketoglutaconate* as a light yellow mobile liquid (0.25 g.), b. p. 93°/0.1 mm. (Found: C, 54.0; H, 6.3. $C_9H_{12}O_5$ requires C, 54.0; H, 6.0%). It reacted instantly with sodium bisulphite solution to form a colourless crystalline mass.

The 2:4-dinitrophenylhydrazone separated from alcohol as deep yellow lustrous leaflets, m. p. 147—148° (Found: C, 47.3; H, 4.4. $C_{15}H_{16}O_8N_4$ requires C, 47.4; H, 4.2%). In an earlier oxidation conducted in toluene the 2:4-dinitrophenylhydrazone, prepared from the crude first distillate, was obtained in red needles from alcohol, m. p. 145—146° (Found: C, 47.4; H, 4.0%). Both forms melted to a bright green liquid.

The absorption spectrum in ether, measured by Dr. F. B. Strauss, showed $\lambda_{max.} = 2280 \text{ \AA.}$, $\epsilon_{max.}^{molar} = 9730$. In methanol ϵ_{molar} was 3670 at 2290 \AA. , and no carbonyl band was found, indicating addition of methanol to the keto group.—DYSON PERRINS LABORATORY, OXFORD. [Received, February 27th, 1946.]

Some New Glycol Mono-ethers. By W. J. DUNSTAN.

In the course of work on bacteriostatic action certain glycol mono-ethers and derivatives were required, and the following appear to be new: (1) 2-*p*-methoxyphenoxyethanol and its *p*-nitrobenzoate; (2) 2-*o*-hydroxymethylphenoxyethanol; (3) *p*-nitrobenzoate of 2-*p*-bromophenoxyethanol.

The glycols were prepared in the usual manner, using ethylene chlorohydrin, sodium ethoxide, and the requisite phenol (Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 164). The *p*-nitrobenzoates were prepared by treating a solution of the substance in dry pyridine with *p*-nitrobenzoyl chloride.

Compound (1) formed white needles, m. p. 70°, from light petroleum (b. p. 60—80°); yield 45% (Found: C, 64.5; H, 7.25. $C_9H_{12}O_3$ requires C, 64.25; H, 7.2%). Its *p*-nitrobenzoate formed pale yellow plates, m. p. 96°, from alcohol (Found: C, 60.5; H, 4.8. $C_{14}H_{15}O_6N$ requires C, 60.5; H, 4.8%).

Compound (2) was isolated as an oil which solidified on standing. Attempts to recrystallise it from carbon tetrachloride gave an oil which solidified on the addition of a drop of water; this solid, m. p. 51°, reliefs on standing in a vacuum desiccator over sulphuric acid, indicating the presence of water of crystallisation; yield 20% (Found: C, 58.2; H, 7.5; H_2O , 9.3. $C_9H_{12}O_3 \cdot H_2O$ requires C, 58.0; H, 7.6; H_2O , 9.7%).

2-*p*-Bromophenoxyethanol (Shukis and Tallman, *J. Amer. Chem. Soc.*, 1944, **66**, 1461) gave a *p*-nitrobenzoate, m. p. 103°, white needles from alcohol (Found: N, 3.85. $C_{15}H_{13}O_5NBr$ requires N, 3.8%).

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The Reduction of *p*-Nitrobenzoic Acid to Hydrazo- and Azo-benzene-4 : 4'-dicarboxylic Acids by Means of Glucose. By MURIEL L. TOMLINSON.

It is well known that *p*-nitrobenzoic acid in alkaline solution is reduced by reagents such as sodium amalgam (Meyer and Dahlem, *Annalen*, 1903, **326**, 335) and sodium stannite (Goldschmidt and Eckardt, *Z. physikal. Chem.*, 1906, **56**, 404) to yield mixtures of azo- and azoxy-benzene-4 : 4'-dicarboxylic acids. Since the free acids are very insoluble substances which decompose at relatively high temperatures, and also since mixtures of their esters crystallise together and simulate pure substances, there was some confusion in the early literature about their identities. Meyer and Dahlem (*Annalen*, 1903, **326**, 331) give what have proved to be authentic descriptions of the acids and their ethyl esters.

Bacharach and Weinstein (*Rec. Trav. chim.*, 1935, **54**, 931) claim to have reduced *p*-nitrobenzoic acid in alkaline solution to azo- and azoxy-benzenedicarboxylic acids by the use of glucose, and they state that the production of the azo- or the azoxy-derivative depends only on the temperature at which the reaction takes place. They characterised their products merely by nitrogen and carboxyl determinations. Repetition of their processes showed that the mixtures, with which they started and which they described as solutions, contain much undissolved sodium *p*-nitrobenzoate, and that their so-called azo- and azoxy-acids gave esters differing in m. p. from those described by Meyer and Dahlem. Further investigation has shown that, under both of the sets of conditions described by Bacharach and Weinstein, the products are mixtures of hydrazobenzene-4 : 4'-dicarboxylic acid (I), first obtained by Bilfinger (*Annalen*, 1865, **135**, 159) and azobenzene-4 : 4'-dicarboxylic acid (II) (Meyer and Dahlem, *loc. cit.*). It has been shown that this reaction can be modified to give good yields of (I) and (II), but under none of the conditions investigated has the azoxy-compound been obtained using glucose as reducing agent. Catalytic reduction of (II) in alkaline solution yields *p*-aminobenzoic acid with the absorption of two mols. of hydrogen per g.-mol., but on similar treatment the products obtained by Bacharach and Weinstein's methods absorbed considerably less than four atoms of hydrogen per mol.

Hydrazobenzene-4 : 4'-dicarboxylic Acid (I).—*p*-Nitrobenzoic acid (13 g.) and sodium hydroxide (50 g.) were mixed in water (225 c.c.) and the solution was warmed to 50°. A solution of glucose (100 g. in 150 c.c. of water) was then added slowly at 50° and the mixture was warmed on a steam-bath until a precipitate started to form. It was then removed and well shaken; the liquid filled with a pale yellow precipitate which soon dissolved to give a brown solution. Air was excluded and the solution was cooled and acidified with acetic acid. The precipitate consisted mainly of (I). It was extracted with hot glacial acetic acid, in which (II) is insoluble, and on cooling the solution deposited colourless needles, m. p. 286° (decomp.) (Found : C, 57.7; H, 4.7; N, 8.7. Calc. for C₁₄H₁₂O₄N₂, C, 57.8; H, 4.8; N, 8.7%). The acetic acid of crystallisation was removed by solution in air-free sodium hydroxide and precipitation with air-free hydrochloric acid (Found : C, 61.9; H, 4.7. Calc. for C₁₄H₁₂O₄N₂ : C, 61.8; H, 4.4%).

Azobenzene-4 : 4'-dicarboxylic Acid (II).—The above process was repeated and then a stream of air was drawn through the brown solution for some hours, until no further precipitate of the sodium salt of (II) was formed; on acidification the mixture deposited (II) (yield, 8–9 g.). Hot potassium carbonate solutions of (II), on cooling, yielded orange needles of the potassium salt of (II) which was recrystallised from water (Found : C, 48.7; H, 2.5; N, 8.0. C₁₄H₈O₄N₂K₂ requires C, 48.6; H, 2.3; N, 8.1%). The acid (II) could not be recrystallised (Found : C, 62.2; H, 3.8; N, 10.6. Calc. for C₁₄H₁₀O₄N₂ : C, 62.2; H, 3.7; N, 10.4%). Catalytic reduction of (II) was not effected, probably because of its insolubility, but aqueous sodium carbonate solutions of (II) were reduced to *p*-aminobenzoic acid (isolated as acetyl derivative) by hydrogen with palladium-charcoal [1 g. of (II) absorbed 182 c.c. of hydrogen at 15°. Calc. for 2 mols., 176 c.c.].

Azobenzene-4 : 4'-dicarboxyl Chloride (III).—This was referred to, but not described, by Einhorn and Uhlfelder (*Annalen*, 1909, **371**, 140); Uspensky's description (*J. Russ. Phys. Chem. Soc.*, 1891, **23**, 93) refers to a mixture of azo- and azoxy-compounds. The acid (II) was refluxed with excess of thionyl chloride for 24 hours, or (II) (1.7 g.) and phosphorus pentachloride (2.9 g.) were heated in *o*-dichlorobenzene (20 c.c.) for 15 minutes, and the precipitate obtained by dilution with light petroleum was recrystallised from light petroleum (b. p. 60–80°), from which *azobenzene-4 : 4'-dicarboxyl chloride* separated as red needles, m. p. 164° (Found : C, 55.1; H, 3.1. C₁₄H₈O₂N₂Cl₂ requires C, 54.7; H, 2.6%). The ethyl ester (IV), m. p. 143°, was obtained when (III) was warmed with alcohol, and the same ester was also obtained (a) by refluxing (II) with alcoholic sulphuric acid for 24 hours, and (b) when equal weights of ethyl *p*-aminobenzoate and ethyl *p*-nitrosobenzoate were heated in alcohol or acetic acid for 1 hour (Found : C, 66.0; H, 5.5; N, 8.6. Calc. for C₁₈H₁₈O₄N₂ : C, 66.3; H, 5.5; N, 8.6%). An alcoholic solution of (IV) (0.3 g.) absorbed 48 c.c. of hydrogen at 23° in the presence of palladium-charcoal (calc. for 2 mols., 45 c.c.). Interruption of reduction when half of this quantity of hydrogen had been taken up yielded the ethyl ester of (I) as colourless needles, m. p. 120° (from alcohol) (Found : C, 65.4; H, 5.9. Calc. for C₁₈H₂₀O₄N₂ : C, 65.9; H, 6.1%). Oxidation of (IV) with hydrogen peroxide in acetic acid for 24 hours at 100° gave ethyl azoxybenzene-4 : 4'-dicarboxylate identical by mixed m. p. determination with that prepared as described by Meyer and Dahlem (*loc. cit.*).

Ethyl p-Nitrosobenzoate.—(Cf. Alway and Pinckney, *Amer. Chem. J.*, 1904, **32**, 399.) Potassium persulphate (8 g.) was mixed with sulphuric acid (6 c.c.) and left for ½ hour. Ice (50 g.) was then added and the solution was neutralised with sodium carbonate crystals. Ethyl *p*-aminobenzoate (2.5 g.) in water (300 c.c.) was added and the solution was left overnight. The precipitate was filtered off, dissolved in ether, and washed with dilute acid; ethyl *p*-nitrosobenzoate was obtained by steam distillation of the residue left after evaporating the ether (Found : C, 60.4; H, 5.0. Calc. for C₉H₉O₃N : C, 60.3; H, 5.0%).

M. p.s are uncorrected.

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