[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. X. SYNTHESIS OF SIMPLE HYDROXYLATED β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES

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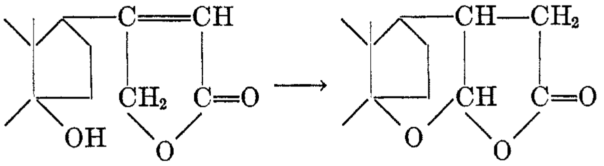
Syntheses of simple unsaturated lactones analogous to the naturally occurring cardiac drugs have been described in previous publications (1, 2), and by application of these methods, such lactones containing steroid ring systems have also been prepared (3). As a result of a study of the properties of the synthetic β-substituted $\Delta^{\alpha,\beta}$-butenolides and comparison of them with the naturally occurring drugs, the conclusion has been reached that the side-chain double bond in the latter is in the α,β-position (4). With this revision in structure, a number of reactions of the natural drugs require amplification before the factors involved become fully understood. Among these, the formation of the so-called iso-aglycones from the aglycones under the influence of alkali (5) is perhaps most interesting. The reaction involved may be represented in an over-all sense by



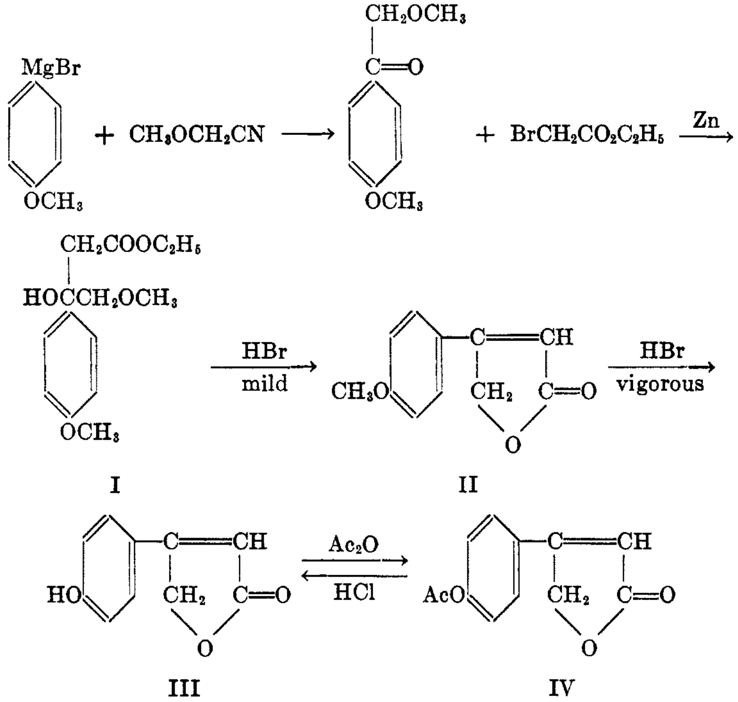
In order to secure the change, it is apparently necessary that a hydroxyl group be located in reactive proximity to carbon atom 21 of the side chain, and, further, that such a hydroxyl group be in the proper stereo-relationship to the side chain.

During the course of pharmacological examination of the simpler lactones, a slight but distinct activity in frogs has been noted in some cases (6). It is of interest, therefore, to prepare several lactones containing different substituent groups on the β-carbon atom of the lactone, in order to ascertain if possible the factors determining cardiotonic activity.

In the present communication we wish to present the results of a study of the synthesis of simple hydroxylated β-substituted $\Delta^{\alpha,\beta}$-butenolides. The study was confined to relatively simple and accessible substances in order that general methods could be worked out, and that the limitations inherent in the present available synthetic methods could be noted. At the same time information bearing on the question of structure and activity was secured. Reactions which can be expected to lead to the three isomeric β-(hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolides have been investigated in detail, and a preliminary study of the corresponding hydroxycyclohexyl butenolides has been started. The latter substances are particularly useful as models for the study of iso-compound formation.

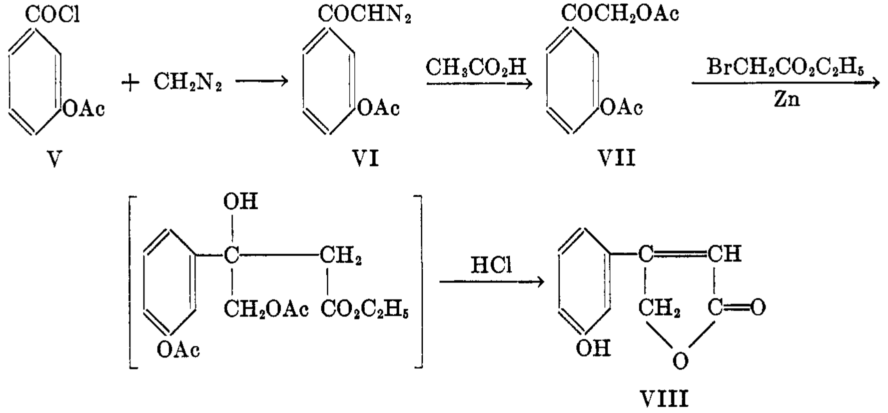
Two general syntheses have been used, that of Rubin, Paist, and Elderfield (1), which proceeds from methoxymethyl ketones, and that of Linville and Elderfield (2), which proceeds from acetoxymethyl ketones. Inasmuch as it is necessary to block any hydroxyl groups present in either synthesis, a choice of ether or acyl blocking groups is thus afforded, and the relative merits of the two procedures will be apparent.

The reactions involved in the preparation of β-(4-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide by the first of the above methods, are shown in the formula scheme.



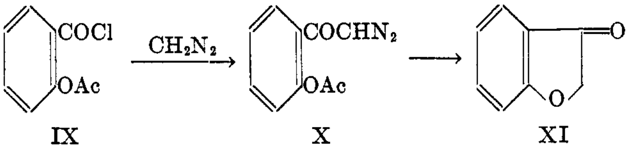
The reactions noted proceeded without difficulty. The ester, I, was converted directly to the unsaturated methoxy lactone, II, by relatively gentle treatment with hydrobromic acid, although the over-all yield appeared to be slightly better if the ester was saponified prior to ring closure of the lactone. More vigorous treatment with hydrobromic acid was necessary to remove the blocking methyl group on the phenolic hydroxyl group. Under the best conditions it was not possible to secure the hydroxy lactone free from contaminating methoxy lactone, and because of the similarity in solubilities of the methoxy lactone, II, and the hydroxy lactone, III, purification of the latter by fractional crystallization was difficult. However, it was possible to prepare the acetoxy lactone, IV, from the mixture of II and III. This was then easily purified, and, on deacetylation by treatment with hydrochloric acid, gave pure β-(4-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The hydroxy lactone as thus obtained gave a strong nitroprusside color test, but no color with ferric chloride. The presence of the phenolic hydroxyl group was shown by acetylation to yield IV, and by methylation with diazomethane to yield II. The lactone also rapidly decolorized an alcoholic solution of bromine.

In view of the difficulty encountered in splitting the blocking ether group in the methoxy lactone (II) the method of Linville and Elderfield (2) appeared to be better adapted for the purpose in hand, inasmuch as the nuclear hydroxyl group could be blocked by an acetyl group. This method was, therefore, used for the preparation of β-(3-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The 4-hydroxyphenyl lactone, III, was also prepared in this way in order to check the products of the two syntheses. The steps in the synthesis of the 3-hydroxyphenyl lactone are shown in formulas V–VIII.



β-(3-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (VIII) gives a strong nitroprusside color test, a red color with ferric chloride, readily decolorizes bromine water, and on methylation with diazomethane, yields the corresponding methoxy lactone. β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide prepared by this method is identical with the lactone prepared from *p*-bromoanisole, and on treatment with diazomethane, yields a methoxy lactone identical with II.

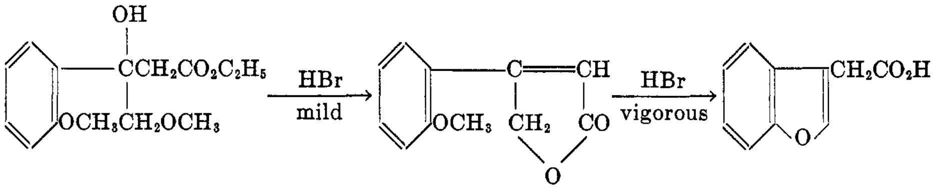
When the preparation of β-(2-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide by either of the above methods was undertaken, it was found that ring closure to coumaranone or derivatives of coumaranone occurred at some stage in the series of reactions under all conditions tried. Acetylsalicylic acid chloride, IX, on treatment with diazomethane apparently yielded the expected diazomethyl ketone, X. However, when X was treated with glacial acetic acid coumaranone, XI, was the only product isolated. The behavior of the reaction mixtures indicated that the desired ω,*o*-diacetoxyacetophenone probably was formed, but underwent ring closure, possibly by loss of acetic anhydride, on working up and attempted purification. This easy ring closure finds a parallel in the observation of Wiedenhagen and Herrmann (7) that *o*-hydroxy-ω-chloroacetophenone yields



coumaranone on treatment with sodium acetate. Likewise Clibbens and Nierenstein (8) found that *o*-acetoxy-ω-chloroacetophenone yields coumaranone on distillation.

In view of the easy removal of the blocking *o*-acetyl group in the reactions discussed above, it was felt that a less easily cleaved ether group might serve better for blocking purposes. Accordingly, *o*-methoxy-ω-diazoacetophenone was prepared. Surprisingly enough, when this was treated with acetic acid, formation of coumaranone proceeded more readily and cleanly than was the case with the acetyl derivative.

Finally the preparation of the desired β-(2-hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide was attempted, starting from ω,*o*-dimethoxyacetophenone. On reaction with ethyl bromoacetate in the presence of zinc, the glycol ether ester, XII, was readily obtained. This gave β-(2-methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide, XIII, when treated in the usual manner. However, all attempts to remove the blocking ether group resulted in the formation of coumaronyl-3-acetic acid, XIV.



XII XIII XIV

In the cyclohexyl series attention has been concentrated on the preparation of β-(2-hydroxycyclohexyl)-$\Delta^{\alpha,\beta}$-butenolide. This substance possesses the desired arrangement of functional groups to serve as a model for studies of the isocompound transformation. For the purpose in mind, salicylic acid or one of its derivatives forms a readily available source of material. No attempt has been made to separate the various stereo and optical isomers encountered, since it was felt that the usefulness of existing synthetic methods could be evaluated with the mixture of isomers, provided analytically pure substances were secured. The resolution of such substances could then be carried out at such a time as the desired synthetic materials had become available. Because of this approach it should be pointed out that in most cases the physical constants of many of the substances encountered are not well defined and represent those of mixtures. Furthermore, failure to secure crystalline derivatives in some cases, as well as the formation of complex mixtures in some reactions may be ascribed to the same cause.

2-Acetoxyhexahydrobenzoic acid chloride apparently reacted normally with diazomethane to yield ω-diazo-2-acetoxyhexahydroacetophenone. However, when the diazo ketone was treated with acetic acid, extensive resinification occurred and no well defined substance could be isolated from the reaction product. It therefore appeared that the acetoxy group was unsuitable for the protection of the nuclear hydroxyl group during the reactions involved. A similar series of reactions proceeding from 2-methoxyhexahydrobenzoic acid was then investigated. Again, while the intermediate diazomethyl ketone appeared to be formed in the normal manner, reaction of the latter with acetic acid again led to unidentifiable compounds.

However a more promising approach to the 2-hydroxycyclohexyl butenolide was opened up by the observation that ethyl β-(*o*-methoxyphenyl)-β-methoxymethylhydracrylate (XII), in contrast to its precursors, could be reduced catalytically with platinum oxide to yield the corresponding cyclohexyl compound, although some cleavage of the ether groups present, and possibly of the ester apparently took place during the reduction. The yield of desired cyclohexyl compound was consequently poor. However in this substance the troublesome steps encountered in the attempts to arrive at it from cyclohexane carboxylic acid and its derivatives have been overcome, and all that remains to be done in order to secure the desired lactone is to split the ether groups and close the lactone in the usual manner. When the cyclohexylhydracrylic ester was treated with hydrobromic acid in acetic acid, conversion of the side chain to the unsaturated lactone apparently occurred, as evidenced by the strong positive Legal test shown by the crude product. However the formation of much tar accompanied the ring closure and it was impossible to isolate more than a fraction of a per cent of product by distillation. Apparently the nuclear hydroxyl group was removed leaving a double bond under this rather severe treatment, with resultant formation of large amounts of resinous substances. Better success attended the use of aqueous hydrochloric acid for cleavage of the ethers and ring closure. When the hydracrylic ester was refluxed with concentrated hydrochloric acid, a substance which gave a strong Legal test and contained chlorine was obtained; this is probably β-(2-chlorocyclohexyl)-$\Delta^{\alpha,\beta}$-butenolide. This was then heated with water in a sealed tube in order to replace the chlorine atom by hydroxyl. The product thus obtained still gave the Legal test, but also still contained chlorine. However the analytical figures obtained indicated that, while the desired replacement of chlorine by hydroxyl had occurred, simultaneously dehydration involving the nuclear hydroxyl group had also taken place to some extent. A suitable synthesis for this type of lactone must remain for future investigation.

None of the lactones described showed cardiac activity when tested in frogs through the kind cooperation of Dr. K. K. Chen of the Lilly Research Laboratories.

EXPERIMENTAL

All melting points are corrected for stem exposure.

ω,4-Dimethoxyacetophenone was prepared from *p*-bromoanisole and methoxyacetonitrile according to the method of Pratt and Robinson (9) who report a yield of 30% (based on the methoxyacetonitrile) of material boiling at 185–190° at 35 mm. and melting at 40°. We obtained a yield of 42% of material boiling at 145° at 7 mm. and melting at 41–42°.

Ethyl β-methoxymethyl-β-(4-methoxyphenyl)hydracrylate (*I*). A mixture of 40.7 g. (0.23 mole) of ω,4-dimethoxyacetophenone, 20.9 g. (0.32 mole) of 20-mesh zinc, and 175 cc. of anhydrous benzene was heated to refluxing. This mixture was stirred vigorously and kept refluxing for 1.25 hours, during which time a solution of 35.0 g. (0.21 mole) of ethyl bromoacetate in 25 cc. of anhydrous benzene was added dropwise. Refluxing and stirring were continued for 3 hours longer. The cooled benzene solution was decanted from the excess zinc, and the zinc was washed with ether. The combined benzene and ether solutions were washed with dilute hydrochloric acid, and dried over anhydrous magnesium sulfate. Distillation yielded 43 g., or 70%, of a slightly yellow viscous oil which boiled at 152–160° at 0.6 mm.

Anal. Calc'd for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5.
Found: C, 63.0; H, 7.8.

When the glycol ether ester was dissolved in glass-distilled alcohol, and shaken with Adams' catalyst in an atmosphere of hydrogen, no hydrogen was absorbed.

β-Methoxymethyl-β-(4-methoxyphenyl)hydracrylic acid. Twenty-eight grams of the above ester was saponified by refluxing for 1.5 hrs. with a solution of 38 cc. of 10% aqueous sodium hydroxide in 40 cc. of absolute alcohol. After distillation of the alcohol, the aqueous solution was washed with ether, acidified with 10% hydrochloric acid, and extracted with ether. This extract was dried over anhydrous magnesium sulfate, and the ether was removed to yield a reddish-yellow oil which soon crystallized. Recrystallization from benzene gave the acid as small white plates which melted at 102.5–103.5°. The yield was 11.5 g. By dissolving the magnesium sulfate with water and recrystallizing the undissolved solid from benzene, an additional 9.5 g. of the acid was obtained. The total yield was 21.0 g. or 84%.

Anal. Calc'd for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7; OCH_3, 25.8.
Found: C, 60.0; H, 6.9; OCH_3, 21.1.

When an alcoholic solution of this acid was shaken with Adams' catalyst in an atmosphere of hydrogen, no hydrogen was absorbed.

β-(4-Methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (II). A mixture of 4.8 g. of the above acid and 16 cc. of glacial acetic acid, which had been saturated with dry hydrogen bromide at 0°, was heated at 110–120° for thirty minutes. When the cooled solution was poured with stirring into 100 cc. of ice-water, a pinkish solid separated. After repeated recrystallization from dilute alcohol the lactone formed very long, thin, white needles which melted at 120°. The yield was 2.0 g. or 53%. This compound gave a positive Legal test and a negative ferric chloride test. An alcoholic solution of it did not decolorize bromine water. It was soluble in chloroform and in hot alcohol, and slightly soluble in ether, benzene, and hot water.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; OCH_3, 16.3.
Found: C, 69.8; H, 5.6; OCH_3, 15.8.

β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (III). A mixture of 2.7 g. of the above methoxy lactone, 23 cc. of a saturated solution of dry hydrogen bromide in glacial acetic acid, 12 cc. of constant boiling hydrobromic acid, and 45 cc. of glacial acetic acid was heated at 120–140° for 3.5 hrs. The solution was concentrated under a partial vacuum, and poured into ice-water to yield 2.0 g. of a chalky solid. After repeated recrystallization from dilute alcohol, with liberal use of decolorizing carbon, feathery clusters of short white needles which melted at 250–256.3° in a sealed tube (the substance decomposed upon heating in an open tube) were obtained. These needles gave a positive Legal test, and a negative ferric chloride test. An alcoholic solution of them decolorized bromine water. The substance has a limited solubility in the ordinary solvents, but is insoluble in choloroform.

A sample which had been purified by vacuum sublimation gave the following analysis, from which the presence of a small amount of methoxy lactone is indicated.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6; OCH_3, 0.0.
Found: C, 68.7; H, 5.1; OCH_3, 2.3.

This same lactone, mixed with the methoxy lactone, was prepared directly from the hydracrylate, (I) in a similar manner. Twenty-six grams of the ester was heated at 130–140° for 3.5 hrs. with a mixture of 100 cc. of acetic acid solution of hydrogen bromide, 100 cc. of constant-boiling hydrobromic acid, and 100 cc. of glacial acetic acid. The reaction mixture was worked up in the same manner as before to yield a purple solid which was dissolved in acetic acid and repeatedly boiled with decolorizing carbon. Removal of the solvent yielded a buff-colored solid which melted from 110–170°. Digestion of this material with hot chloroform gave two fractions. The insoluble fraction was recrystallized from alcohol and formed white needles which melted at 247–257.4°. The melting point was not depressed when the substance was mixed with the lactone (III), prepared as above. The yield was 5.0 g. or 28%. The chloroform-soluble fraction was recrystallized from dilute alcohol to yield 6.5 g., or 34% of white needles, which melted at 118–119.5°, and which gave no melting point depression when mixed with the methoxy lactone, (II) prepared from the acid.

β-(4-Acetoxyphenyl)-$\Delta^{\alpha,\beta}$*-butenolide (IV).* The impure hydroxy lactone obtained as above was treated in the usual manner with acetic anhydride and fused sodium acetate. Upon pouring the deep red solution into ice-water a reddish liquid, which solidified upon stirring, separated. After repeated recrystallization from dilute methanol, long white needles which melted at 138.6–140.7° were obtained. This compound gave a positive Legal test.

Anal. Calc'd for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6.
Found: C, 66.0; H, 4.9.

This acetate was hydrolyzed by warming for one minute with an equal volume of concentrated hydrochloric acid, and the product was recrystallized once from dilute alcohol. The pure hydroxy lactone formed white needles which melted at 260.5–263.6° and gave no melting point depression with the hydroxyphenyl lactone obtained as described below.

p-*Acetoxybenzoic acid* was prepared from *p*-hydroxybenzoic acid according to the method of Chattaway (10) who reports a 93% yield of material melting at 189–190°. We obtained a yield of 91% of material melting at 186.1°.

p-*Acetoxybenzoyl chloride* was prepared by heating the above acid with 3 cc. of thionyl chloride per gram of the acid for six hours at 50°. After removal of the excess thionyl chloride, using anhydrous benzene, the material was stored in sealed glass ampoules without further purification.

ω,4-Diacetoxyacetophenone. This substance was prepared from the acid chloride, by slowly adding a dry ether solution of the latter to an ethereal solution of excess diazomethane to form the diazomethyl ketone, which was then treated with glacial acetic acid. A 65% yield (based on the acid used) of crude yellow plates which melted at 93.2–94.6° was obtained. After repeated recrystallization from benzene, white diamond-shaped plates melting at 94.6–95.6° were obtained. Robertson and Robinson (11) report the melting point 98° for this compound prepared from ω-chloro-4-hydroxyacetophenone. The crude material is very unpleasant to work with as it causes the skin to sting and burn.

β-(4-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$*-butenolide (III).* A solution of 7.5 g. of the above ketone in 30 cc. of anhydrous benzene was added to 3.3 g. of 20-mesh zinc, and the mixture was heated to refluxing. A solution of 5.3 g. of freshly distilled ethyl bromoacetate in 10 cc. of anhydrous benzene was dropped in over a period of 15 min. After refluxing for another 30 min., the zinc and the walls of the flask had become coated with a yellow solid which was not dissolved by addition of fresh benzene and which stopped the reaction. After removing the benzene *in vacuo* the product was separated from the zinc by use of 20% hydrochloric acid. The decantate from the zinc contained suspended solid material which was warmed on the steam-bath for one minute with an equal volume of concentrated hydrochloric acid and then poured into ice-water. The precipitate thus obtained was recrystallized from 95% alcohol to yield 2.3 g. or 41% of white needles which melted at 262.5–263.5° in a sealed tube.

This material gave a strong Legal test and was proved, by mixed melting point, to be the same as that prepared as above.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6.
Found: C, 68.1; H, 4.8.

The methoxy lactone which was prepared by treating an acetone solution of the hydroxy lactone with diazomethane melted at 119–120° and proved to be identical with that prepared as above.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; OCH_3, 16.3.
Found: C, 69.7; H, 5.4; OCH_3, 13.8.

m-*Acetoxybenzoic acid* was prepared from *m*-hydroxybenzoic acid according to the method of Chattaway (10). A 90% yield of material melting at 128.7–131.3° was obtained. Herzig and Titchatschek (12) report the acid as melting at 127–129°.

m-*Acetoxybenzoyl chloride* was prepared from the acid according to Hayashi (13) except for the fact that a heating period of 2.5 hrs. was found to be necessary instead of the 30 min. heating period given by him. The excess thionyl chloride was removed and the product was sealed in glass ampoules.

ω,3-Diacetoxyacetophenone was prepared by reaction between the acid chloride and diazomethane to yield the diazomethyl ketone, which was then heated for 2.5 hrs. on a boiling water-bath with glacial acetic acid. A 68% yield of a viscous yellow oil which boiled at 155–158° at 0.5 mm. was obtained. Hayashi (13) using a 20 min. heating period in a similar procedure, reports a 57% yield of a yellow oil which boiled at 189–197° at 14 mm.

β-(3-Hydroxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide. The above ketone was condensed with ethyl bromoacetate in the same manner as before, except that alcohol was used to dissolve the gum which formed on the zinc. The resulting mixture was decanted from the excess zinc and concentrated *in vacuo* to yield a thick paste, which was then mixed with 100 cc. of 10% hydrochloric acid and heated on a boiling water-bath for 10 min. The clear red solution was poured, with stirring, into 250 cc. of ice-water, and the solid which separated was filtered off and washed with cold water. This crude product (34% yield) had a strong coumarin-like odor. After repeated recrystallization from methanol and washing with ether, a yield of 23% of odorless, slightly yellow, rectangular plates which melted at 187.5–188.5° (in a sealed tube) was obtained. The lactone was more soluble in the usual solvents than the para isomer. It gave a positive Legal test. An aqueous solution gave a positive ferric chloride test and also decolorized bromine water.

Anal. Calc'd for $C_{10}H_8O_3$: C, 68.2; H, 4.6.
Found: C, 68.5; H, 4.7.

β-(3-Methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide was prepared in the same manner as was the para isomer. After three recrystallizations from dilute alcohol and two from water, it formed white needles which melted at 86.3–87.3°. The methoxy lactone gave a positive Legal test and a negative ferric chloride test.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3.
Found: C, 69.3; H, 5.4.

o-*Acetoxybenzoyl chloride* (*IX*) was prepared from *o*-acetoxybenzoic acid by the same procedure as was used in the preceding series.

ω-Diazo-2-acetoxyacetophenone (*X*) was prepared from the acid chloride in the usual manner and was not further purified. An attempt at hydrolysis, in which a dioxane solution of the diazomethyl ketone was heated at 50° with 10% sulfuric acid, yielded coumaranone (XI) (see later).

Attempted preparation of ω,2-diacetoxyacetophenone. When the above diazomethyl ketone was treated with glacial acetic acid according to the usual procedure, a dark red oil was obtained. Since this material could not be crystallized, it was distilled at 2 mm. A small portion distilled, crystallizing in the side arm of the flask, but the residue remained as a red tar which could not be identified. The distillate was recrystallized from isopropyl alcohol to form white needle-like plates which melted at 101–102° and was identified as coumaranone (XI), by mixed melting point. Clibbens and Nierenstein (8) obtained the same product by distillation of ω-chloro-2-acetoxyacetophenone and report the melting point 101–102°.

Anal. Calc'd for $C_8H_6O_2$: C, 71.6; H, 4.5.
Found: C, 71.5; H, 4.7.

In another attempt to form the diacetoxyacetophenone, the diazomethyl ketone was mixed with glacial acetic acid and was allowed to stand at room temperature for one week. As bubbles of gas were evolved when concentrated hydrochloric acid was added to a test portion, thus showing the presence of unreacted diazomethyl ketone, the reaction mixture was then heated on a boiling water-bath for 1.5 hrs. The reaction mixture was worked up in the same manner as before to yield a red oil which did not crystallize when seeded with a sample of the coumaranone obtained previously. However, when this oil was washed with ether, a dark red solid was obtained which upon recrystallization from benzene formed orange needles which melted at 204–205°. This material was not further investigated.

Anal. Found: C, 67.6; H, 4.0.

Steam distillation of the ether washings yielded a small amount of coumaranone. The residue from the steam distillation was distilled to yield a yellow oil which boiled at 149–152° at 0.5 mm., and which quickly turned red upon standing. The bulk of the material remained in the flask in the form of a red tar. The distillate gave a positive ferric chloride test and dissolved in 10% aqueous sodium hydroxide with the formation of a dark red solution from which a red oil was obtained upon acidification with hydrochloric acid, but which could not be identified.

Other attempts, in which the diazomethyl ketone was treated with a saturated solution of fused sodium acetate in glacial acetic acid, produced similar results.

*Methyl-*o*-methoxybenzoate* was prepared by methylation of methyl salicylate with dimethyl sulfate and sodium hydroxide by a modification of the method of Sachs and Herold (14) which consisted of dropwise simultaneous addition to the methyl salicylate, with heating and stirring, of the sodium hydroxide solution and the dimethyl sulfate. A 71% yield of the ester, which boiled at 132–133° at 15 mm., was obtained. Sachs and Herold report a yield of 80–90% of material boiling at 252° at atmospheric pressure. When the Sachs and Herold procedure was attempted, the reaction invariably became violent and got out of hand.

o*-Methoxybenzoic acid* was prepared by alkaline hydrolysis of the above pure ester, or by hydrolysis of the crude reaction mixture. In the latter case, the procedure of Graebe (15) was used to separate it from salicylic acid by means of the calcium salt. The material melted at 100.6–102.5°. Cohen and Dudley (16) report the melting point 99–101°.

o*-Methoxybenzoyl chloride* was prepared from the acid according to the procedure of Fischer and Slimmer (17), and was sealed in glass ampoules after removal of the excess thionyl chloride.

ω-Diazo-2-methoxyacetophenone was prepared in the usual manner from the acid chloride. The yellow oil was used immediately without purification.

Reaction of ω-diazo-2-methoxyacetophenone with acetic acid. When acetic acid was mixed with the diazomethyl ketone at room temperature, a violent exothermic reaction immediately took place, and coumaranone crystallized from the reaction mixture. When this reaction mixture was worked up, only coumaranone was obtained.

When glacial acetic acid was added to an ether solution of the diazomethyl ketone, which was cooled in a cold water-bath, the reaction proceeded smoothly. After standing at room temperature for forty hours, a 75% yield of coumaranone was obtained.

ω,2-Dimethoxyacetophenone. *o*-Methoxyphenylmagnesium bromide was prepared from 100 g. of *o*-bromoanisole and magnesium according to the usual Grignard procedure. After refluxing the reaction mixture for one hour, it was cooled to room temperature, and a solution of 38.4 g. of methoxyacetonitrile in 200 cc. of sodium-dried ether was added with mechanical stirring over a period of one hour. At first a white solid separated, but soon a black gum formed which made stirring very difficult. However, upon stirring and refluxing for an additional 2 hrs. this gum disappeared leaving a creamy yellow mixture. The ether was then replaced with anhydrous benzene, and refluxing was continued for 2.5 hrs. The brown mixture was cooled, hydrolyzed with 10% sulfuric acid, and worked up in the usual manner, to give a yield of 52 g., or 54% of material which boiled at 149–152° at 10 mm. Pratt and Robinson (18) prepared this compound from *o*-methoxybenzoyl chloride and report a yield of 44% of material which boiled at 165° at 15 mm. The semicarbazone melted at 138.1–139.1°. Pratt and Robinson report the melting point 137° for this derivative.

Ethyl β-methoxymethyl-β-(2-methoxyphenyl)hydracrylate was prepared from the ketone by the same procedure used in the para series. The ester was obtained in 74% yield and boiled at 127–128° at 0.2 mm. The colorless oil gradually became yellow upon standing. It gave a negative Legal test. Saponification by the usual procedure gave an oil which could not be crystallized.

β-(2-Methoxyphenyl)-$\Delta^{\alpha,\beta}$*-butenolide.* A solution of 21 g. of the above ester in 40 cc. of glacial acetic acid and 80 cc. of the acetic acid-hydrogen bromide mixture was heated at 110–120° for 30 min., and then worked up in the usual manner. After repeated recrystallization from benzene, a 51% yield of colorless, needle-like rectangular prisms which melted at 95.1–95.6° was obtained. This lactone gave a positive Legal test and a negative ferric chloride test. Neither an alcoholic solution nor an aqueous suspension of the lactone decolorized bromine water.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3.
Found: C, 69.2; H, 5.2.

Action of hydrogen bromide on β-(2-methoxyphenyl)-$\Delta^{\alpha,\beta}$*-butenolide.* Many attempts were made to split the ether in the above methoxy lactone by use of hydrobromic acid, of hydrogen bromide in glacial acetic acid, and of mixtures of these with one another or with glacial acetic acid, under various heating conditions, but in all cases a mixture of the starting material and an acidic substance which proved to be coumaronyl-3-acetic acid was obtained. After recrystallization from petroleum ether (Skellysolve B) the latter formed flattened white needles which melted at 89.2–91.2°. Titoff, Müller, and Reichstein (19) report the melting point 89–90°. The *amide* was prepared in the usual manner and was recrystallized from ether to yield long, flattened needles which melted at 190.6–191.1°. Reichstein and co-workers report the melting point 191° for this derivative.

Ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate. A solution of 27 g. of ethyl β-(*o*-methoxyphenyl)-β-methoxymethylhydracrylate in 150 cc. of glass-distilled glacial acetic acid was shaken under 3 atm. pressure of hydrogen with 0.5 g. of platinum oxide. Absorption of hydrogen proceeded slowly and after 48 hrs. 0.5 g. of fresh catalyst was added. After about 60 hrs. absorption of hydrogen stopped after the calculated amount had been taken up. The reduction product was dissolved in ether and washed with sodium carbonate solution which removed a small amount of acidic materials. The neutral material was very carefully fractionally distilled under reduced pressure and a fraction of 15.4 g. of material boiling at 104–114° at 0.3 mm. followed by a second fraction of 7.9 g. boiling at 114–116° was collected. Redistillation of the second fraction yielded a colorless oil boiling at 122–123° at 1 mm. The analytical figures obtained with this material indicated that it was the desired ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate.

Anal. Calc'd for $C_{14}H_{26}O_5$: C, 61.3; H, 9.5; Alkoxyl O, 17.5.
Found: C, 61.6; H, 9.4; Alkoxyl O, 15.1.

The lower-boiling fractions had higher carbon and lower hydrogen contents, indicating that some formation of hexahydrocoumaronyl derivatives by ester cleavage had taken place, an assumption which was supported by the lower alkoxyl oxygen content of these fractions. For example, a fraction boiling at 116–120° at 1 mm. gave the following figures:

Anal. Found: C, 63.4; H, 9.9; Alkoxyl O, 12.4.

Action of hydrochloric acid on ethyl β-methoxymethyl-β-(2-methoxycyclohexyl)hydracrylate. A solution of 3.8 g. of the above ester in 12 cc. of hydrochloric acid (sp. gr. 1.19) was refluxed for 3 hrs. After about 10 min. an oil separated. The cooled reaction mixture was extracted with chloroform, and the chloroform solution was washed successively with dilute sodium carbonate solution and water. After removal of the solvent a dark oil remained which contained chlorine and gave a strong Legal test. In order to replace the chlorine by hydroxyl, the oil was heated in a sealed tube at 120° with 30 cc. of water for 2 hrs. The reaction mixture was extracted with ether and the product still showed a faint Beilstein test for halogen and a strongly positive Legal test. It was distilled under reduced pressure and the fraction boiling at 185–195° at 0.1 mm. was collected as a nearly colorless oil. Analysis indicated that some dehydration of the nuclear hydroxyl group had occurred.

Anal. Calc'd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7.
Calc'd for $C_{10}H_{12}O_2$: C, 73.2; H, 7.3.
Found: C, 68.4; H, 7.9.

When hydrobromic acid was used instead of hydrochloric acid for the above reaction, decomposition was more pronounced and an extremely small yield of product was obtained, which, however, gave a strong positive Legal test.

Methyl 2-methoxycyclohexane carboxylate. Methyl *o*-methoxybenzoate was dissolved in absolute methanol and hydrogenated in the presence of Raney Nickel, at 200° and 2000–2700 pounds per square inch pressure of hydrogen. Variation of the temperature or of the concentration of the solution did not appreciably alter the results, but the pressure must initially be high in order to get reaction. The catalyst was removed by centrifuging, and the reaction mixture was distilled, yielding 30% of material which boiled at 96.5–97° at 15 mm.

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.8; H, 9.4.
Found: C, 62.8; H, 9.3.

The main product of the reaction was methyl cyclohexane carboxylate.

2-Methoxycyclohexane carboxylic acid. This acid was obtained by alkaline hydrolysis of the ester, in a yield of 83%, as a colorless viscous oil which boiled at 122–123° at 5 mm. It had an odor which resembled that of valeric acid.

Anal. Calc'd for $C_8H_{14}O_3$: C, 60.7; H, 8.9; OCH_3, 19.6.
Found: C, 60.9; H, 9.1; OCH_3, 19.8.

The *p*-toluidide was prepared in the usual manner, as a red oil which crystallized on addition of petroleum ether. After six recrystallizations from this solvent, it formed fine white needles which melted at 130.2–132.4°.

Anal. Calc'd for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6.
Found: C, 73.1; H, 8.7.

The mother liquors yielded a small amount of white needles which melted at 85–108°, and were probably a mixture of the *cis* and *trans* isomers. Further purification was not possible with the small amount of material available.

2-Methoxycyclohexane carboxylic acid chloride was prepared from the acid in the usual manner andwas sealed in glass ampoules without further purification.

ω-Diazo-2-methoxyhexahydroacetophenone was prepared from the above acid chloride according to the usual procedure and was obtained as a red oil which was used immediately without purification.

Attempted preparation of ω-acetoxy-2-methoxyhexahydroacetophenone. The diazomethyl ketone was treated with acetic acid, according to the usual procedure, and the red oil obtained was distilled three times to yield two colorless fractions. A yield of 4.8 g. of material which boiled at 88–90° at 10 mm., and of 1.5 g. of material which boiled at 93–105° at 10 mm. was obtained from 17.6 g. of the diazomethyl ketone. Analysis of both of these fractions indicated a mixture of hexahydrocoumaranone and ω-acetoxy-2-methoxyhexahydroacetophenone.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5.
Calc'd for $C_8H_{12}O_2$: C, 68.5; H, 8.6.
Found: C, 67.0, 67.4; H, 8.8, 8.9.

Ethyl hexahydrosalicylate was prepared by high-pressure hydrogenation of an ethanol solution of methyl salicylate in the presence of Raney Nickel catalyst according to Connor and Adkins (20) who obtained material which boiled at 117–18° at 13 mm. We obtained material which boiled at 110–115° at 13 mm.

Hexahydrosalicylic acid. The above ester was shaken at room temperature with a slight excess of 10% aqueous sodium hydroxide solution for about 5 minutes. The resulting hemogeneous solution was allowed to stand for 1.5 hrs. after which it was concentrated *in vacuo*, washed with ether, acidified with a slight excess of 10% hydrochloric acid, saturated with ammonium sulfate, and finally thoroughly extracted with ether. Removal of the ether gave a quantitative yield of a syrup which was crystallized with great difficulty. This material was apparently a mixture of *cis* and *trans* isomers, which caused difficulty in recrystallization, as it tended to separate as an oil from the solvents. After repeated recrystallization from dry ether and from ethyl acetate, two fractions of transparent prisms were obtained. The larger fraction melted at 76–78°, and the other melted at 109–110°. Einhorn and Meyenburg (21), who prepared this acid from hexahydroanthranilic acid, report the melting point 111°, as do all other investigators who have made it with the exception of Böeseken and his co-workers (22), who state that they obtained a small amount of an acid which melted from 57–63° from the mother liquors of the 111° acid.

Anal. of the material which melted at 76–78°. Calc'd for $C_7H_{12}O_3$: C, 58.3; H, 8.4.
Found: C, 58.1; H, 8.2.

The *amide* was prepared in the usual manner from the ester and concentrated ammonium hydroxide. After several recrystallizations from acetone, it formed rectangular plates which melted at 113.7–114.7°.

Anal. Calc'd for $C_7H_{13}NO_2$: C, 58.7; H, 9.2.
Found: C, 58.8; H, 9.1.

2-Acetoxycyclohexane carboxylic acid. A crude sample of the above acid, melting at 51–91°, was dissolved in anhydrous ether and was gently refluxed for 1.5 hrs. with an excess of freshly distilled acetyl chloride. Distillation caused some decomposition, but a yield of 21% of a syrup which boiled at 132–135° at 4 mm. was obtained. This syrup crystallized after standing overnight, and after several recrystallizations from petroleum ether formed prisms which melted at 66.1–66.6°. When a sample of this material was mixed with a sample of the original acid, it liquified before it could be placed in a melting point tube. Easson and Pyman (23) describe the acetate as melting at 96–101°.

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.1; H, 7.6.
Found: C, 58.1; H, 7.7.

Attempts at purification, without distillation, by seeding and recrystallization of the crude syrup were partially successful, but the process was very time consuming.

The p*-toluidide* was prepared in the usual manner, from the crude acid, by way of the acid chloride. Repeated recrystallization from petroleum ether gave two fractions; the larger fraction formed white needles which melted at 154–155.9°, and the smaller fraction formed white needles which melted at 124–143°.

Anal. of the first fraction. Calc'd for $C_{16}H_{21}NO_3$: C, 69.8; H, 7.7.
Found: C, 70.2; H, 8.0.

2-Acetoxycyclohexane carboxylic acid chloride was prepared in the usual manner by the action of thionyl chloride at room temperature upon crude acid. Distillation caused partial decomposition, but a yield of 30% of material which boiled at 100–107° at 4 mm. was obtained. Preparation of the *p*-toluidide gave a mixture which was identical with that obtained above.

ω-Diazo-2-acetoxyhexahydroacetophenone was prepared from the above acid chloride in the usual manner.

Attempted preparation of ω,2-diacetoxyhexahydroacetophenone. The diazomethyl ketone was treated with acetic acid in the usual manner, yielding a red oil. Distillation caused some decomposition, and the bulk of the material remained in the flask as a red tar, but a very small amount of a yellow liquid distilled at 80–120° at 0.4 mm. This material soon turned dark red upon standing. Further investigation of this substance was abandoned because of the extremely small yield.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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