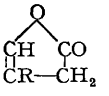
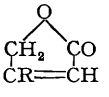
152. *The Synthesis of Some Unsaturated γ-Lactones.*

By G. Swain, A. R. Todd, and W. S. Waring.

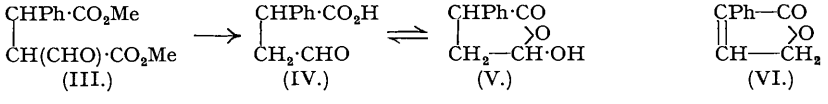
With a view to gain insight into the structural features essential to the physiological activity of the cardiac glycosides, a number of unsaturated γ-lactones bearing simple cyclic substituents in the α-, β-, or γ-positions have been prepared. In the case of the α- and β-substituted compounds all those obtained were $\Delta^{\alpha\beta}$-butenolides, although their mode of preparation from substituted β-formylpropionic acids might have been expected to give $\Delta^{\beta\gamma}$-butenolides. In the γ-substituted series $\Delta^{\beta\gamma}$-butenolides were readily obtained by lactonising γ-keto-acids. A number of the lactones prepared have been examined for digitalis-like action. None of those examined showed any activity in cats although some caused systolic arrest of the frog heart. This is in accord with the published findings of other investigators working on similar lines.

Although it is known that the unsaturated γ-lactone grouping in the steroid aglycones of the cardiac glycosides plays a dominant part in determining the physiological activity of the natural drugs, the mechanism of their action on the heart is unknown. At the time when the investigations now described were commenced (1939) no evidence was available as to the part, if any, played by the steroid nucleus in the action of these substances. It seemed therefore of interest to attempt the synthesis of compounds containing a similar unsaturated lactone grouping attached to simpler ring systems in the hope of obtaining information on this point and, perhaps, of preparing comparatively simple substances with cardiotonic properties similar to those of the natural drugs. When much of the work described in this paper had been carried out, several publications dealing with similar synthetic studies appeared (Elderfield *et al.*, *J. Org. Chem.*, 1941, **6**, 261, 270, 273, 289; 1942, **7**, 374, 444), together with others describing analogous work in the steroid series (Ruzicka, Reichstein, and Fürst, *Helv. Chim. Acta*, 1941, **24**, 76; Elderfield *et al.*, *J. Org. Chem.*, 1942, **7**, 362, 383). Circumstances have delayed for some time the completion and publication of our studies. We now wish to record our results; although in two cases the same compounds have been prepared by Elderfield and his collaborators, we have, in general, employed different synthetic methods. Until 1941, the accepted structure of the cardiac aglycones of the *Digitalis–Strophanthus* group, put forward largely on the basis of the investigations of Jacobs and of Tschesche, was represented by (I), where R is a steroid nucleus variably substituted. According to this view, they were β-substituted $\Delta^{\beta\gamma}$-butenolides and it was to the synthesis of such compounds and of corresponding α- and γ-substituted lactones that we first directed our attention. During the course of our work a re-examination of the natural aglycones by Paist, Blout, Uhle, and Elderfield (*J. Org. Chem.*, 1941, **6**, 273) has shown that structure (I) is erroneous and that they are in fact β-substituted $\Delta^{\alpha\beta}$-butenolides (II).

(I.)  (II.) 

All our attempts to obtain α- or β-substituted $\Delta^{\beta\gamma}$-butenolides by lactonising the corresponding α- or β-substituted β-formylpropionic acids failed; in every case migration of the double bond occurred and the products were $\Delta^{\alpha\beta}$-butenolides. The preparation of γ-substituted $\Delta^{\beta\gamma}$-butenolides, on the other hand, was readily effected by lactonising the appropriate γ-keto-acids.

(a) *α-Substituted Lactones.*—In our first experiments we endeavoured to prepare α-phenyl-$\Delta^{\beta\gamma}$-butenolide by the following route. Methyl phenylsuccinate was formylated readily by ethyl formate and sodium, but the product gave analytical values suggesting that it was a mixture of methyl β-formyl-α-phenylsuccinate (III) with the corresponding diethyl or methyl ethyl esters formed by ester interchange during formylation; in accordance with this view hydrolysis, which was accompanied by decarboxylation, gave β-*formyl-α-phenylpropionic acid* (IV), characterised as its 2 : 4-*dinitrophenylhydrazone*.



(III.) (IV.) (V.) (VI.)

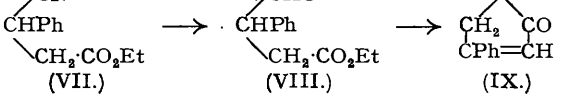
The acid (IV) distilled as a thick liquid which, on standing, set to a sticky solid; it was insoluble in cold sodium carbonate solution but dissolved slowly in sodium hydroxide. In view of this, and of the facts that it did not reduce Tollens's reagent and gave only a faint colour in the Legal test (alkaline sodium nitroprusside), it seems probable that the acid exists mainly in the form of the isomeric hydroxy-lactone (V). Several unsuccessful attempts were made to dehydrate the aldehydo-acid (IV) by means of acetic anhydride, piperidine, dimethylaniline and triethanolamine. Eventually, lactonisation was achieved by using hydrobromic acid in acetic acid, although the yield of lactone was low and much phenylsuccinic acid was formed. The lactone reduced Tollens's reagent and gave a positive Legal test, but its absorption spectrum showed a maximum at 2565 A. (ε = 9820), indicating that the double bond in the lactone ring was conjugated with the aromatic nucleus; it is therefore to be regarded as α-*phenyl-*$\Delta^{\alpha\beta}$*-butenolide* (VI). No trace of the $\Delta^{\beta\gamma}$-isomer was obtained. The possibility that the initial formylation of methyl phenylsuccinate might have led to methyl α-formyl-α-phenylsuccinate rather than (III), and that the final product of the synthesis might accordingly have been β-phenyl-$\Delta^{\alpha\beta}$-butenolide (IX), was ruled out by the synthesis of (IX) by an unambiguous route (see below). The lactone (VI) was also obtained by heating *methyl γγ-dimethoxy-α-phenylbutyrate* with hydrobromic acid in

acetic acid, but the yield was no greater than with the free aldehydo-acid. During attempts to dehydrate (IV) with acetic anhydride, a saturated lactone was obtained, which, on the basis of its analysis and properties, we regard as *γ-acetoxy-α-phenylbutyrolactone* formed by acetylation of the isomeric form (V) of the aldehydo-acid.

Since the physiological activity of the cardiac aglycones is enhanced and, in some therapeutically important respects, modified by glycosidic combination with sugars in the natural drugs, it was desirable that efforts be made to obtain a lactone analogous to (VI) containing a hydroxyl group which might serve as a point of attachment for a sugar residue. To this end we endeavoured to apply the method described above, starting with 4-hydroxyphenylsuccinic acid, which was prepared in good yield from ethyl α-cyano-4-acetoxycinnamate by addition of hydrogen cyanide and subsequent hydrolysis of the crude ethyl αβ-dicyano-β-(4-acetoxyphenyl)-propionate. Attempted formylation of *methyl 4-acetoxyphenylsuccinate* gave only syrupy, unidentifiable products. Methyl 4-methoxyphenylsuccinate, however, was formylated smoothly by ethyl formate and sodium, yielding a mixture of methyl and ethyl β-formyl-α-(4-methoxyphenyl)succinates which, on hydrolysis, gave a product whose behaviour indicated it to be a mixture of the expected aldehydo-acid and the tautomeric hydroxy-lactone analogous to (IV) and (V). For purposes of characteristisation, the 2 : 4-*dinitrophenylhydrazone* of the acid was prepared but the main bulk of material was not further purified and was heated directly with hydrobromic acid in acetic acid in the hope that simultaneous lactonisation and demethylation might occur. The product was, however, α-(4-*methoxyphenyl*)-$\Delta^{\alpha\beta}$-*butenolide* and we were unable to effect demethylation under conditions which did not simultaneously disrupt the lactone ring.

Stobbe (*J. pr. Chem.*, 1914, **89**, 329) prepared a mixture of ethyl Δ^1-*cyclo*pentenylsuccinate and ethyl *cyclo*pentylidenesuccinate by condensing *cyclo*pentanone with ethyl succinate in presence of sodium ethoxide; a similar condensation using *cyclo*hexanone followed by hydrolysis gave Δ^1-cyclo*hexenylsuccinic acid*, which was readily hydrogenated to *cyclo*hexylsuccinic acid. *Methyl* cyclo*hexylsuccinate* reacted with ethyl formate in presence of sodium to give, by analogy with the corresponding case of the phenylsuccinate, a mixture of methyl and ethyl esters of β-formyl-α-*cyclo*hexylsuccinic acid which on hydrolysis and decarboxylation yielded β-*formyl*-α-cyclo*hexylpropionic acid*. This acid reduced Tollens's reagent only on warming, and on being heated with hydrobromic acid in acetic acid it gave α-cyclo*hexyl*-$\Delta^{\alpha\beta}$-*butenolide* as a colourless mobile liquid which reduced Tollens's reagent in the cold and gave a positive Legal reaction.

(b) β-*Substituted Lactones*.—In the first instance it was decided to attempt the synthesis of β-phenyl-$\Delta^{\beta\gamma}$-butenolide (I; R = Ph) by the action of hydrobromic acid and acetic acid on *ethyl* β-*formyl*-β-*phenylpropionate* (VIII), prepared by reduction of ethyl β-phenyl-β-cyanopropionate (VII) by Stephen's method. Torrey, Kuck, and Elderfield (*J. Org. Chem.*, 1941, **6**, 289) have, since this preparation was carried out, reported the synthesis of (VIII) by this method to be impracticable, but although the yield in the reduction is not high,



the starting material is readily accessible and no serious difficulties were encountered by us. The ester (VIII) was characterised as its 2 : 4-dinitrophenylhydrazone, m. p. 129—130°. Torrey, Kuck, and Elderfield (*loc. cit.*) prepared this derivative from a specimen of aldehydo-ester obtained by hydrogenation of impure ethyl β-formyl-β-phenylpropenoate, and record m. p. 108·5—109°. It is difficult to understand this discrepancy in m. p. unless it be due to dimorphism, although we found no evidence for the existence of two forms. Treatment of (VIII) with hydrobromic acid in acetic acid gave β-phenyl-$\Delta^{\alpha\beta}$-butenolide (IX); that the double bond occupied the αβ- and not the βγ-position followed from the presence in the absorption spectrum of a maximum of high intensity at 2730 A. (ε = 20,500). This is in accord with the results of Elderfield and his co-workers, who have also prepared (IX) by a different route (Rubin, Paist, and Elderfield, *J. Org. Chem.*, 1941, **6**, 261), and also failed to obtain the corresponding $\Delta^{\beta\gamma}$-butenolide.

Attempts to extend the method used for the synthesis of (IX) to β-(4-hydroxyphenyl)-$\Delta^{\alpha\beta}$-butenolide met with little success. *Ethyl 4-acetoxybenzylidenemalonate* reacted readily with potassium cyanide to give *ethyl* β-*cyano*-β-(4-*acetoxyphenyl*)*propionate*, although some hydrolysis of the acetoxy-group occurred during the reaction, and the product had to be reacetylated before it could be crystallised. No trace of aldehyde was obtained when efforts were made to reduce the cyano-ester by Stephen's method. It was hoped that *ethyl* β-*cyano*-β-(4-*methoxyphenyl*)*propionate*, prepared in similar fashion from ethyl anisylidenemalonate, might be reduced more readily, but only traces of aldehyde were obtained. In view of these results this method of approach was not further pursued. A specimen of β-(4-methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide was, however, prepared by carrying out a Reformatsky reaction with ω-acetoxy-4-methoxyacetophenone and ethyl bromoacetate and treating the product with hydrobromic acid. This method is analogous to that used by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 270) for the preparation of β-phenyl-$\Delta^{\alpha\beta}$-butenolide, and indeed the synthesis of β-(4-methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide by a similar method was subsequently described by Marshall, Kuck, and Elderfield (*J. Org. Chem.*, 1942, **7**, 444).

(c) *γ-Substituted Lactones*.—In order to have available a range of unsaturated lactones varying in the nature and position of substituents, several γ-substituted $\Delta^{\beta\gamma}$-butenolides were prepared. On heating

β-(4-*hydroxybenzoyl*)*propionic acid* with acetic anhydride, a product was obtained which, purified by sublimation in a vacuum, had the properties expected of γ-(4-*acetoxyphenyl*)-$\Delta^{\beta\gamma}$-*butenolide*. Lactonisation of β-(4-methoxyphenyl)propionic acid in the same manner gave γ-(4-*methoxyphenyl*)-$\Delta^{\beta\gamma}$-*butenolide*.

In the naphthalene series γ-(2-*acetoxy*-6-*naphthyl*)-$\Delta^{\beta\gamma}$-*butenolide* was obtained by heating β-(2-hydroxy-6-naphthoyl)propionic acid with acetic anhydride. For the preparation of this acid, 2-ethoxynaphthalene—a supply of which happened to be available—was condensed with succinic anhydride by means of aluminium chloride in nitrobenzene. In addition to β-(2-hydroxy-6-naphthoyl)propionic acid, β-(2-*ethoxy*-6-*naphthoyl*)-*propionic acid* and β-(2-*ethoxy*-1-*naphthoyl*)*propionic acid* were isolated from the reaction. Although β-(2-ethoxy-6-naphthoyl)propionic acid could be readily de-ethylated, β-(2-ethoxy-1-naphthoyl)propionic acid when heated with hydrobromic acid in acetic acid gave only β-naphthol. Exactly similar behaviour in this and other respects was shown by β-(2-methoxy-1-naphthoyl)propionic acid (Short, Stromberg, and Wiles, J., 1936, 320), a sample of which was kindly supplied by Dr. W. F. Short for comparison.

Several of the lactones described in this paper as well as aconic acid (β-carboxy-$\Delta^{\beta\gamma}$-butenolide) were examined pharmacologically for digitalis-like action. These tests were carried out by Dr. J. Raventos in the Biological Department of Messrs. Imperial Chemical Industries Ltd., Blackley, and to him we are greatly indebted.

The following lactones were tested on cats by intravenous injection, the auricular and ventrical contractions being simultaneously recorded: α-phenyl-$\Delta^{\alpha\beta}$-butenolide (30 mg./kg.), β-phenyl-$\Delta^{\alpha\beta}$-butenolide (15 mg./kg.), γ-phenyl-$\Delta^{\beta\gamma}$-butenolide (100 mg./kg.), γ-(2-acetoxy-6-naphthyl)-$\Delta^{\beta\gamma}$-butenolide (25 mg./kg.), aconic acid (20 mg./kg.). None of them showed any digitalis-like interference with the conduction of impulses. On the other hand, when tested on the isolated frog heart by perfusion in Ringer solution by the inferior *venæ cavæ*, α-*cyclo*hexyl-$\Delta^{\alpha\beta}$-butenolide caused systolic arrest after 5 mins. at a dilution of 1 in 2000; slight action could be detected at a dilution of 1 in 10,000. α-Phenyl-$\Delta^{\alpha\beta}$-butenolide, γ-(4-acetoxyphenyl)-$\Delta^{\beta\gamma}$-butenolide, and aconic acid were virtually devoid of activity in the frog test.

More extended pharmacological examination was not made as the above results appeared to be rather similar to those recorded by other workers who have examined a considerable range of synthetic unsaturated lactones (Chen, Steldt, Fried, and Elderfield, *J. Pharm. Exp. Ther.*, 1942, **74**, 381; Chen and Elderfield, *ibid.*, 1942, **76**, 81; Krayer, Mendez, Espanés, and Linstead, *ibid.*, 1942, **74**, 372). From their results and our own it would seem that, although quite a number of synthetic non-steroid unsaturated lactones, including such simple compounds as methyl coumalate, may cause systolic arrest of the frog heart, none so far prepared shows the characteristic action of the cardiac glycosides or agylcones on the mammalian heart. It is doubtful whether in this case the frog test is of any value in assessing digitalis-like activity of synthetic compounds.

Experimental.

Formylation of Methyl Phenylsuccinate.—Methyl phenylsuccinate (33 g.; Anschütz, *Annalen*, 1907, **354**, 128) was dissolved in dry ether (150 c.c.), and ethyl formate (16·8 g.) and sodium wire (4·0 g.) added. The flask was closed by a calcium chloride tube and set aside at room temperature. Little visible reaction occurred at first but after 3 days all the sodium had disappeared and a brown resin had separated which dissolved on addition of water (250 c.c.). The ethereal layer was discarded, and the aqueous layer acidified and extracted with ether. The extract was washed, dried, evaporated, and the thick oily residue distilled under reduced pressure. The formylation product was obtained as a colourless syrupy liquid (16 g.), b. p. 130—135°/0·3 mm. (bath temp. 160—170°) [Found: C, 63·2; H, 6·1. $C_9H_8O(CO_2Me)_2$ requires C, 62·4; H, 5·6%].

β-Formyl-α-phenylpropionic Acid.—The above product (15·0 g.), dissolved in glacial acetic acid (50 c.c.), was refluxed for 3 hours with hydrochloric acid (50 c.c., *d* 1·16). The cooled solution was partly neutralised with sodium hydroxide (20 g. in 300 c.c. of water), saturated with salt, and extracted with ether. The ethereal solution was washed several times with aqueous sodium carbonate (10%), the combined washings acidified with hydrochloric acid, and the oil which separated taken up in ether and dried over sodium sulphate. The syrupy residue (10·0 g.) left after removal of the ether was distilled under reduced pressure. *β-Formyl-α-phenylpropionic acid* (5·7 g.) was obtained as a viscous, colourless syrup, b. p. 137—142°/0·02 mm. (bath temp. 175—180°) in which some solid separated on prolonged standing. A redistilled specimen set slowly to a sticky solid, m. p. 49—51° (Found: C, 67·1; H, 5·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The distilled product was insoluble in cold sodium carbonate solution, dissolved slowly in cold sodium hydroxide, did not reduce Tollens's reagent, and gave only an extremely weak, transient maroon in the Legal test. (Light absorption in alcohol: max. at 2580 A., ε = 194.) The acid gave a 2 : 4-*dinitrophenylhydrazone*, which crystallised from acetic acid in orange prisms, m. p. 216—218° (decomp.) (Found: C, 53·4; H, 4·0; N, 15·1. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9; N, 15·6%). The 2 : 4-dinitrophenylhydrazone has the curious property of crystallising either in yellow prisms or in mixtures of yellow and orange prisms; both forms have the same m. p.

γ-Acetoxy-α-phenylbulyrolactone.—β-Formyl-α-phenylpropionic acid (2·0 g.) was refluxed for 20 hours with acetic anhydride (7 c.c.). Excess of anhydride was decomposed with water, and the product extracted with ether. The orange oil (1·5 g.) left after removal of ether distilled at 160—170° (bath temp.)/0·01—0·02 mm. as a pale greenish-yellow syrup, which solidified on standing and was then recrystallised from aqueous methanol. *γ-Acetoxy-α-phenylbutyrolactone* separated in colourless prismatic plates, m. p. 84—85° (Found: C, 65·2; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). The purified lactone did not reduce Tollens's reagent and gave no colour in the Legal test. The crude distillate, however, partly reduced Tollens's reagent and showed an intense violet changing through maroon to orange-brown in the Legal reaction.

α-Phenyl-$\Delta^{\alpha\beta}$-butenolide.—β-Formyl-α-phenylpropionic acid (10 g.), dissolved in acetic acid (20 c.c.), was heated under reflux for 4 hours with a solution of hydrobromic acid in acetic acid (50 g. saturated at 0°). The product was poured into water, extracted with ether, and the extract thoroughly washed, dried over sodium sulphate, and evaporated. The brown oily residue (3·7 g.) was distilled under a pressure of 5×10^{-3} mm. (bath temp. 120—130°). The colourless distillate (1·8 g.) solidified, and then crystallised from benzene–light petroleum (1 : 1) in colourless plates (1·4 g.), m. p. 89° (Found: C, 75·1; H, 5·1. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%). The *lactone* reduced Tollens's reagent almost immediately and showed an intense violet rapidly changing through maroon to orange-brown in the Legal test. (Light

absorption in alcohol : max. 2565 A., ε = 9820.) The sodium carbonate washings on acidification yielded an oil (1·6 g.) from which phenylsuccinic acid was isolated.

Methyl γγ-Dimethoxy-α-phenylbutyrate.—β-Formyl-α-phenylpropionic acid (3·0 g.), dissolved in dry methanolic hydrogen chloride (16 c.c. of 1%), was allowed to stand for 12 hours at room temperature, then refluxed for 15 minutes and set aside for a further 48 hours. The product was poured into potassium carbonate solution (100 c.c. of 5%), and the oil which separated taken up in ether. The residue (3·3 g.) left after removal of the ether was distilled under reduced pressure. *Methyl γγ-dimethoxy-α-phenylbutyrate* (2·9 g.) was obtained as a colourless oil, b. p. 114—115°/0·1—0·2 mm. (Found : C, 65·8; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). It gave an intense violet rapidly changing to yellow in the Legal test and reduced Tollens's reagent rapidly at room temperature. *Action of hydrobromic acid in acetic acid.* The ester (3 g.) was refluxed for 4 hours with a solution of hydrobromic acid in acetic acid (15 c.c. of 33%). The product was poured into water, extracted with ether, and washed with sodium carbonate solution (5%). The neutral fraction (0·3 g.) recovered from the ether was distilled at 75°/10^{-4} mm., and the crystalline distillate (0·1 g.) recrystallised from benzene–light petroleum (1 : 1). α-Phenyl-$\Delta^{\alpha\beta}$-butenolide was obtained in colourless plates, m. p. 89°, undepressed in admixture with the specimen already described.

Methyl 4-Hydroxyphenylsuccinate.—4-Hydroxyphenylsuccinic acid (138 g.; Chrzaszczewska, *Chem. Zentr.*, 1926, **97**, 2, 2906) was esterified by refluxing for 2¼ hours with methanolic hydrogen chloride (1100 c.c. of 4%). The *ester*, worked up in the usual manner and recrystallised from benzene–light petroleum (3 : 1), formed colourless prisms, m. p. 76—77°. Dave and Nargund (*J. Univ. Bombay*, 1938, **7**, 196), give b. p. 150—160°/0·20 mm. (Found : C, 60·9; H, 5·8. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 5·9%). Acetylation of the ester by refluxing with acetic anhydride for 2 hours gave *methyl 4-acetoxyphenylsuccinate*, which crystallised from aqueous alcohol in colourless needles, m. p. 55° (Found : C, 60·0; H, 5·8. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%). Attempts to condense this product with ethyl formate and sodium failed.

4-Methoxyphenylsuccinic Acid.—To methyl 4-hydroxyphenylsuccinate (2·8 g.) dissolved in 10% sodium hydroxide solution methyl sulphate (3 c.c.) was added, and the mixture heated on a steam-bath for 1 hour with frequent shaking. More methyl sulphate (3 c.c.) was added together with more sodium hydroxide, and heating continued for another hour. Acidification of the hot solution caused the separation of a crystalline precipitate of 4-methoxyphenylsuccinic acid (1·9 g.). This was filtered off, and after two crystallisations from hot water, had m. p. 201° (Found : C, 59·0; H, 5·5; MeO, 13·3; equiv., 112. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4; 1MeO, 13·8%; equiv., 112). This acid has been described by various workers, who record m. p.'s ranging from 191° (Chrzaszczewska, *loc. cit.*) to 207—208° (Corson and Stoughton, *J. Amer. Chem. Soc.*, 1928, **50**, 2825).

Methyl 4-Methoxyphenylsuccinate.—Methyl 4-hydroxyphenylsuccinate (11·9 g.) and methyl iodide (7·1 g.) were dissolved in acetone and refluxed with anhydrous potassium carbonate for 2½ hours. More methyl idodide (7·1 g.) was added, and refluxing continued for 4½ hours longer. Water was then added, and the precipitated oil taken up in ether. The ethereal solution was washed with alkali, then water, and dried over sodium sulphate. Removal of the solvent left an oil (10·7 g.), which distilled completely between 130—135°/10^{-3} mm. as a colourless liquid (Found : C, 62·0; H, 6·6. Calc. for $C_{13}H_{16}O_5$: C, 61·9, H, 6·4%). Corson and Stoughton (*loc. cit.*), who prepared this ester by a different route, describe it as a solid, m. p. 93—94°, for which they could get no consistent analytical figures.

α-(4-Methoxyphenyl)-$\Delta^{\alpha\beta}$-butenolide.—Methyl 4-methoxyphenylsuccinate (20 g.) and ethyl formate (12 g.) were dissolved in dry ether (200 c.c.) and allowed to react with sodium wire at room temperature for 3 days. Water was added to dissolve the resinous product, and the alkaline solution separated. Acidification and extraction with ether yielded a viscous red oil (11·4 g.), which distilled as a thick, clear yellow liquid at 165°/5 × 10^{-2} mm. This product was evidently a mixture of the methyl and the ethyl ester [Found : C, 62·3; H, 6·2. Calc. for $C_{10}H_{10}O_2(CO_2Me)_2$: C, 60·0; H, 5·7%].

The formylation product (7·8 g.) was refluxed with a mixture of glacial acetic acid(25 c.c.) and concentrated hydrochloric acid (20 c.c.) for 3½ hours. The reaction mixture was partly neutralised with sodium hydroxide, extracted with ether, and the extract washed several times with dilute sodium cabonate solution. The carbonate washings were acidified, the precipitated oil taken up in ether, and the solution washed, dried, and evaporated. A dark oil was left (4·6 g.), which distilled at 180°/2 × 10^{-3} mm. as a thick orange-coloured liquid. It neither reduced Tollens's reagent nor gave a colour with ferric chloride, but a weak brown colour developed in the Legal reaction. From this behaviour, and evidence of a lacto-group during titration, it would seem that the aldehydo-acid exists largely in the form of the isomeric hydroxylactone. The crude acid was converted without further purification into the unsaturated lactone. Treatment of the oil with 2 : 4-dinitrophenylhydrazine in the usual way gave *β-formyl-α-(4-methoxyphenyl)propionic acid* 2 : 4-*dinitrophenylhydrazone*, m. p. 156—157° (Found : N, 14·8. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

The crude aldehydo-acid (2 g.) was refluxed with a mixture of glacial acetic acid (7 c.c.) and a solution of hydrobromic acid in acetic acid (20 c.c. of 50%) for 4 hours. Water was then added, and the mixture extracted with ether. The ethereal solution, after being washed with water and sodium bicarbonate solution, was finally dried over sodium sulphate, and the solvent removed. An oil (400 mg.) was left which partly crystallised on standing for several days. It was purified by dissolving it in ether and shaking the solution with very dilute sodium hydroxide to remove traces of phenols. After removal of the solvent, the residue was sublimed in a molecular still. The crystalline sublimate, which was not very soluble in ether, crystallised from benzene containing a little light petroleum in colourless plates, m. p. 123—124°. It reduced Tollens's reagent in the cold, and gave a positive Legal reaction (Found : C, 69·4; H, 5·3. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). Light absorption in alcohol : max. 2790 A. (ε, 14,000).

Δ^1-cyclo*Hexenylsuccinic Acid.*—Alcohol-free sodium ethoxide, prepared from molecular sodium (23 g.) and dry alcohol (46 g.) in benzene, was cooled in an ice–salt mixture, *cyclo*hexanone (84 g.) and succinic ester (87 g.) added, and the reaction mixture diluted with dry ether (50 c.c.). The reaction vessel was kept in an ice-box for 3 days, after which the reaction was allowed to proceed at room temperature. At the end of two weeks, water was added to the mixture. The solid dissolved, and the aqueous layer was separated and almost neutralised with sulphuric acid. The weakly alkaline solution, after being repeatedly extracted with ether to remove succinylsuccinic ester (14 g.), was made strongly acid with sulphuric acid, which precipitated a heavy brown oil (132 g.). This was separated, and heated with continuous stirring for 45 mins. with excess of barium hydroxide solution, the temperature being maintained just below the b. p. The insoluble barium salt was collected, decomposed with hot dilute hydrochloric acid, and the oily acid taken up in ether, the solution dried over sodium sulphate, and the solvent removed. The oily residue (75 g.) was triturated with cold xylene, the crude *acid* being left as a white powder (36 g.). Recrystallisation from hot water (charcoal) gave colourless prisms (35 g.), m. p. 146—147° (Found : C, 60·4; H, 7·3; equiv., 100. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%; equiv., 99). *cyclo*Hexylidenesuccinic acid has m. p. 175° (Ingold, Seeley, and Thorpe, J., 1923, **123**, 853), and unlike our product gives *cyclo*hexanone on oxidation with permanganate.

cyclo*Hexylsuccinic Acid.*—*cyclo*Hexenylsuccinic acid (35 g.), hydrogenated in methano solution by means of a platinum oxide catalyst, absorbed 4 l. of hydrogen (Calc. for 1 double bond : 3·9 l.). Removal of methanol and recrystallisation from hot water gave *cyclo*hexylsuccinic acid as colourless plates, m. p. 146—147° (depressed on admixture with *cyclo*hexenylsuccinic acid) (Found : C, 59·6; H, 8·2. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). Naps and Johns (*J. Amer Chem. Soc.*, 1940, **62**, 2450) give m. p. 146°.

Methyl cyclo*Hexylsuccinate.*—*cyclo*Hexylsuccinic acid (35 g.) was esterified by refluxing with methanol (250 c.c.

containing concentrated sulphuric acid (10 g.) for 4 hours. The *ester* distilled at 110—120°/10^{-1} mm. as a mobile, colourless liquid (34 g.) (Found : C, 63·2; H, 9·1. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

Formylation of Methyl cyclo*Hexylsuccinate.*—Methyl *cyclo*hexylsuccinate (21 g.) and ethyl formate (12 g.), dissolved in dry ether (200 c.c.), were allowed to react with sodium wire (2·5 g.) at room temperature for 3 days. Water (100 c.c.) was added to dissolve the resinous solid which had been formed, and the aqueous alkaline layer was separated and acidified. The precipitated oil was extracted with ether, the solution washed with dilute sodium carbonate and water, dried, and the solvent removed. The residual oil distilled at 125°/10^{-3} mm. as a colourless liquid (6·8 g.) which gave an intense maroon colour with ferric chloride [Found : C, 61·5; H, 8·0. $C_9H_{14}O(CO_2Me)_2$ requires C, 60·9; H, 7·8%].

*β-Formyl-α-*cyclo*hexylpropionic Acid.*—The above formylation product (6·5 g.) was refluxed with a mixture of glacial acetic acid (25 c.c.) and concentrated hydrochloric acid (15 c.c.) for 3½ hours. The solution, after being partly neutralised with sodium hydroxide, was extracted with ether, and the ethereal solution extracted with aqueous sodium carbonate (10%). The carbonate extract was acidified, and the precipitated oil taken up in ether, the solution dried and evaporated, acetic acid being removed by heating at 100°/12 mm. The residue was distilled in a high vacuum, and the product, a viscous colourless liquid (3·5 g.), b. p. 140—150°/10^{-2} mm., rapidly crystallised in the receiver. Recrystallisation from light petroleum (b. p. 40—60°) gave fine colourless needles, m. p. 66—67°, which reduced Tollens's reagent on warming, but gave no reaction with ferric chloride, or in the Legal reaction (Found : C, 65·3; H, 8·6; equiv., 183. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7; equiv., 184).

*α-*cyclo*Hexyl-Δ$^{\alpha\beta}$-butenolide.*—The above aldehydo-acid (3·3 g.) was lactonised by refluxing with hydrobromic acid in glacial acetic acid for 4 hours. The reaction mixture was poured into water, extracted with ether, the ethereal extract washed with 5% sodium carbonate solution and water, dried over sodium sulphate, and the solvent removed. The *lactone* distilled at 120°/0·5 mm. as a mobile, colourless liquid (1·67 g.) which reduced Tollens's reagent, and gave a positive Legal reaction (Found : C, 72·6; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%).

Ethyl β-Formyl-β-phenylpropionate.—Dry hydrogen chloride was passed into a stirred suspension of finely powdered anhydrous stannous chloride (57 g.) in dry ether (400 c.c.) until two liquid layers were obtained. Ethyl β-cyano-β-phenylpropionate (40·6 g.; Bredt and Kallen, *Annalen*, 1896, **293**, 343) in ether (30 c.c.) was added slowly with rapid stirring. The mixture was refluxed for 2 hours, resaturated with hydrogen chloride, and allowed to stand overnight. A small amount of solid had separated, and the mixture was refluxed for 8 hours, again saturated with hydrogen chloride, and kept overnight. This was repeated three times. A further quantity of ether (100 c.c.) was then added, and the mixture cooled in ice-salt and saturated with hydrogen chloride. The suspended solid (30 g.) was filtered off, and decomposed by warming to 70° with water (100 c.c.) for 30 mins. The oil which separated was extracted with ether, and the extract washed and dried over sodium sulphate. Removal of the ether left a pale yellow oil (10 g.) which was distilled under reduced pressure. *Ethyl β-formyl-β-phenylpropionate* was obtained as a colourless liquid (7·2 g.), b. p. 85—90°/0·1 mm. (Found : C, 69·4; H, 6·9. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). It reduced Tollens's reagent at room temperature, but gave no colour in the Legal test. It gave a 2 : 4-*dinitrophenylhydrazone*, which separated from methanol in slender, yellow needles, m. p. 129—130° (Found : C, 56·1; H, 4·7; N, 14·3. $C_{18}H_{18}O_6N_4$ requires C, 56·0; H, 4·7; N, 14·5%).

β-Phenyl-Δ$^{\alpha\beta}$-butenolide.—Ethyl β-formyl-β-phenylpropionate (2·2 g.) in acetic acid (4 c.c.) was heated under reflux for 2 hours with concentrated hydrochloric acid (4 c.c.). The mixture was cooled, poured into excess of sodium carbonate solution (10%), and extracted with ether. The solvent was removed, and the residual sticky solid recrystallised from aqueous methanol. The lactone separated in colourless prisms, m. p. 97°; Rubin, Paist, and Elderfield (*loc. cit.*) give m. p. 94° (Found : C, 74·7; H, 5·2. Calc. for $C_{10}H_8O_2$: C, 75·0; H, 5·0%). It reduced Tollens's reagent immediately at room temperature, and gave a crimson colour in the Legal test. Light absorption in alcohol : max. at 2730 A. (ε, 20,500).

Ethyl 4-Acetoxybenzylidenemalonate.—*p*-Hydroxybenzaldehyde (6 g.), malonic ester (8 g.), acetic anhydride (12 c.c.), and piperidine (0·2 c.c.) were heated together in a sealed tube at 140—150° for 20 hours. The product was poured into water and the solid which separated was recrystallised from aqueous methanol. *Ethyl 4-acetoxybenzylidenemalonate* formed colourless prisms (7·5 g.), m. p. 67—68° (Found : C, 62·5; H, 5·8. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%).

Ethyl β-Cyano-β-(4-acetoxyphenyl)propionate.—Ethyl 4-acetoxybenzylidenemalonate (36·6 g.) was dissolved in alcohol (250 c.c.) at 30°, and a solution of potassium cyanide (8 g.) in water (15 c.c.) added. The temperature was maintained at 60° for 6 hours, and the precipitate of potassium bicarbonate filtered off (5·3 g.). After standing overnight, the solution was heated to 65° for 4 hours, and a further quantity of bicarbonate (1·8 g.) removed. The solution was then diluted with water (1·5 l.), acidified, and extracted 5 times with ether. The ethereal solution was washed with sodium carbonate and water, dried over sodium sulphate, and the solvent removed. A viscous syrup (24 g.) remained, which was soluble in sodium hydroxide and did not crystallise. The product was therefore acetylated by heating for 30 mins. with acetic anhydride (100 c.c.). The mixture was poured into water and kept until the oil solidified. *Ethyl β-cyano-β-(4-acetoxyphenyl)propionate* crystallised from ether–light petroleum (1 : 1) in feathery needles (24 g.), m. p. 82° (Found : C, 64·2; H, 5·8. $C_{14}H_{15}O_4N$ requires C, 64·3; H, 5·8%). Attempts to reduce this ester by Stephen's method failed to yield any aldehyde.

Ethyl β-Cyano-β-(4-methoxyphenyl)propionate.—Ethyl anisylidenemalonate (25 g.; Knoevenagel and Groos, *Ber.*, 1898, **31**, 2594) in alcohol (150 c.c.) was treated with a solution of potassium cyanide (6 g.) in water (12 c.c.) and heated at 60° for 11 hours. Precipitated potassium bicarbonate (6·3 g.) was filtered off, and the filtrate poured into water and worked up in the usual manner. The *cyano-ester* distilled at 140°/10^{-2} mm. as a colourless liquid (16 g.) (Found : C, 67·6; H, 6·7; N, 5·9. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). Reduction of the ester by Stephen's method gave only traces of aldehyde.

β-(4-Methoxyphenyl)-Δ$^{\alpha\beta}$-butenolide.—Ethyl bromoacetate (9·2 g.), ω-acetoxy-4-methoxyacetophenone (10·4 g.; Tiffeneau, *Compt. rend.*, 1910, **150**, 1182), and zinc (7 g.) in dry benzene (70 c.c.) were warmed gently until reaction set in. After the initial reaction had subsided, the mixture was refluxed for 2½ hours with stirring, The mixture was then treated with water and dilute hydrochloric acid, and extracted with benzene. The benzene solution was washed, dried over sodium sulphate, and evaporated. The residual yellow oil (6·8 g.), which presumably contained ethyl β-(4-methoxyphenyl)-β-acetoxymethylhydracrylate, was refluxed with a solution of hydrobromic acid in acetic acid for 1 hour to effect lactonisation. The mixture was poured into water, extracted with benzene, the solution dried, and the solvent removed. The residual dark oil (4 g.), heated at 110°/10^{-2} mm., gave a sublimate of crystals mixed with some yellow oil. Crystallisation from benzene yielded pale yellow needles, m. p. 121—122°, which reduced Tollens's reagent and gave a purple colour in the Legal reaction. The absorption spectrum showed maxima at 2250 A. (ε, 16,000) and 3020 A. (ε, 32,000). Marshall, Kuck, and Elderfield (*loc. cit.*) give m. p. 120° for β-(4-methoxyphenyl)-Δ$^{\alpha\beta}$-butenolide prepared by a similar route starting from ω : 4-dimethoxyacetophenone.

β-(4-Hydroxybenzoyl)propionic Acid.—β-(4-Methoxybenzoyl)propionic acid (5 g.) (Rosenmund and Shapiro, *Arch. Pharm.*, 1934, **272**, 318) in a solution of hydrobromic acid in glacial acetic acid (20 c.c. of 33%) was refluxed for 3 hours, and then poured into water. After standing overnight, the dark brown crystalline product was filtered off (1·7 g.) and purified by repeated crystallisation from hot water (charcoal). It was finally recrystallised from benzene–acetone, and obtained as colourless needles, m. p. 159—160° (Found : C, 62·2; H, 5·3. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

γ-(4-Acetoxyphenyl)-Δ$^{\beta\gamma}$-butenolide.—A mixture of β-(4-hydroxybenzoyl)propionic acid (8 g.) and acetic anhydride (60 c.c.) was refluxed for 1 hour, and then poured into water. After standing overnight, the solid was filtered off, dried, and sublimed in a vacuum. The sublimate was a white powder, which, however, crystallised from benzene as salmon-pink needles. Resublimation gave colourless needles (2·8 g.), m. p. 123—124° (Found: C, 66·3; H, 4·9. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). The substance reduced Tollens's reagent, and gave a positive Legal reaction. The absorption spectrum in alcohol showed a maximum at 2650 A. (ε, 13,000).

γ-(4-Methoxyphenyl)-Δ$^{\beta\gamma}$-butenolide.—β-(4-Methoxybenzoyl)propionic acid (1·5 g.) and acetic anhydride (5 c.c.) were refluxed for 1½ hours, and then poured into water. After standing for a short time the red solid was collected, dissolved in ether, and the solution washed with sodium bicarbonate solution and then with water, dried, and the solvent removed. The residue sublimed at 100°/5 × 10^{-3} mm. as a white solid (0·6 g.). Attempts to purify it by crystallisation from ordinary solvents were unsatisfactory on account of gradual decomposition. It was finally obtained as a white crystalline powder, m. p. 110°, by repeated vacuum sublimation (Found: C, 68·7; H, 5·1; CH_3O, 16·1. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3; CH_3O, 16·3%). It reduced Tollens's reagent in the cold, and the Legal test produced a transient green coloration passing rapidly through brown to deep red.

2-Ethoxy-6-naphthoylpropionic Acid, 2-Ethoxy-1-naphthoylpropionic Acid, and 2-Hydroxy-6-naphthoylpropionic Acid.—Aluminium chloride (80 g., 2 mols.) was powdered and dissolved in nitrobenzene (260 g.), and the solution cooled to 10°. Finely powdered succinic anhydride (33 g., 1·1 mols.) was stirred in, and the mixture cooled to 0° in an ice-salt bath. 2-Ethoxynaphthalene (51·6 g., 1 mol.), dissolved in nitrobenzene (65 c.c.) at 10°, was added to the stirred mixture during 1¼ hours. Stirring was continued at 0° for 2 hours, and at room temperature for a further 5 hours. After standing for 3 days, the green oil was poured on a mixture of ice (500 g.) and hydrochloric acid (200 c.c., *d* 1·16), and the mixture was then warmed to 40° in order to facilitate separation of the nitrobenzene from the aqueous layer which was rejected. The nitrobenzene was removed in steam, and the green viscous residue dissolved in sodium carbonate solution (300 c.c. of 10%) at 35°. Salt (100 g.) was added but the precipitated sodium salts could not be filtered off satisfactorily, and were therefore redissolved by addition of water (500 c.c.). The solution, containing a little suspended material, was washed thrice with ether. Some solid separated at the interface and was removed by filtration (A). This solid was dissolved in water, the solution filtered, and the filtrate acidified. The white, crystalline solid which separated (3·9 g.) was recrystallised from aqueous alcohol (60%) and finally from alcohol. 2-Hydroxy-6-naphthoylpropionic acid was obtained in small, colourless plates, m. p. 229—231° (Found: C, 69·0; H, 4·9. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 5·0%). Robinson and Thompson (J., 1938, 2012) give m. p. 235°. The 2 : 4-*dinitrophenylhydrazone* separated from benzene–alcohol (1 : 1) in small red prisms, m. p. 216—217° (Found: N, 12·8. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

The aqueous filtrate after removal of (A) was acidified with concentrated hydrochloric acid and the oily brown solid which separated was collected, washed with water, and the moist filter cake dissolved in hot methanol (180 c.c.). On cooling, brown prisms (24·5 g.; m. p. 135—140°) were deposited. Recrystallisation from ethyl acetate (charcoal) gave *2-ethoxy-6-naphthoylpropionic acid* (14 g.) as colourless prisms, m. p. 162—163° (Found: C, 71·1; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). It was characterised as the 2 : 4-*dinitrophenylhydrazone*, which separated from ethyl acetate in orange-red, feathery needles, m. p. 171—172° (Found: N, 11·6. $C_{22}H_{20}O_7N_4$ requires N, 12·4%).

Concentration of the methanolic mother-liquors yielded a further small amount of slightly oily crystalline solid (5·6 g., m. p. 125—130°). This was recrystallised, the solvent being the ethyl acetate mother-liquors of the 2-ethoxy-6-naphthoylpropionic acid, and, by fractionation, *2-ethoxy-1-naphthoylpropionic acid* (5·0 g.) was finally obtained in colourless prisms, m. p. 164—165° (depression to 140° in admixture with the 2 : 6-isomer) (Found: C, 70·7; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). No 2 : 4-dinitrophenylhydrazone could be obtained. A specimen of 2-methoxy-1-naphthoylpropionic acid (kindly supplied by Dr. W. F. Short) did not form a 2 : 4-dinitrophenylhydrazone under similar conditions.

De-ethylation of 2-Ethoxy-6-naphthoylpropionic Acid.—The ethoxy-acid (1·0 g.) was heated under reflux for 3¼ hours with aqueous acetic acid (10 c.c. of acid + 5 c.c. of water) and hydrobromic acid (10 c.c. of a 50% solution in acetic acid). On cooling, the reddish-brown solution deposited a solid (0·7 g.), which was recrystallised first from aqueous alcohol and finally from alcohol–ethyl acetate. 2-Hydroxy-6-naphthoylpropionic acid separated in small colourless plates, m. p. 229—231°, undepressed in admixture with the specimen already described.

De-ethylation of the isomeric 2-ethoxy-1-naphthoylpropionic acid in a similar manner gave β-naphthol, m. p. 120—121°. 2-Methoxy-1-naphthoylpropionic acid behaved in exactly the same way.

γ-(2-Acetoxy-6-naphthyl)-Δ$^{\beta\gamma}$-butenolide.—2-Hydroxy-6-naphthoylpropionic acid (1·0 g.) was refluxed for 2 hours with acetic anhydride (10 c.c.). The solution became deep orange red. Acetic anhydride was decomposed by addition of excess of water, and the reddish-brown precipitated solid was filtered off, washed with water, dried, and sublimed at 120—140°/10^{-4} mm. The colourless crystalline sublimate (0·4 g., m. p. 135—142°) was recrystallised from ethyl acetate, giving *γ-(2-acetoxy-6-naphthyl)-Δ$^{\beta\gamma}$-butenolide* as faintly pink plates, m. p. 158—160° (sintering at 150°) (Found: C, 72·2; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·7; H, 4·5%). The lactone reduced Tollens's reagent immediately at room temperature and gave a crimson colour in the Legal test. It became coloured on exposure to light and air or on boiling its solutions in common organic solvents—especially in alcohol.

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