

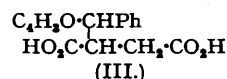
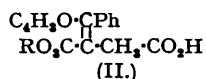
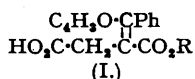
#### 48. Intramolecular Ring Closures with cis- and trans- $\gamma$ -Phenyl- $\gamma$ -(2-furyl)itaconic Acid.\*

By EDWARD B. KNOTT.

cis- and trans- $\gamma$ -Phenyl- $\gamma$ -(2-furyl)itaconic acid have been prepared by the condensation of ethyl succinate with phenyl 2-furyl ketone. The cis-acid has been cyclised to 4-hydroxy-7-phenylcoumarone-2-carboxylic acid and 1-keto-3-(2'-furyl)indene-2-acetic acid, both of which give 2-hydroxy-9-keto-3':2':3:4-furofluorene on further cyclisation. The trans-acid underwent ring closure to 1-hydroxy-4-(2'-furyl)naphthalene-3-carboxylic acid.

THE synthesis of 1-hydroxy-4-phenylnaphthalene-3-carboxylic acid was effected by Borsche and his school (*Annalen*, 1936, 526, 1) by intramolecular ring closure of the monoester of  $\gamma\gamma$ -diphenylitaconic acid. The cyclisation of the dibasic acid was achieved by Stobbe and Vieweg (*Ber.*, 1902, 35, 1727), who obtained 1-keto-3-phenylindene-2-acetic acid, which was cyclised by Borsche (*loc. cit.*) to 2-hydroxy-3:4-benzfluorenone. This fluorenone has now been found to function as a colour coupler, giving on development of a photographic emulsion with dialkyl-*p*-phenylenediamines a black dye image. It was thought to be of interest, therefore, to prepare other fluorenones of this type.

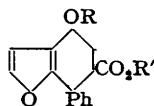
This work follows the same line of reactions as the above, but by the replacement of one of the phenyl groups of the itaconic acid by a furyl group, two isomeric itaconic acids were to be expected which could lead to two series of cyclisation products. The initial materials were obtained by the condensation of phenyl 2-furyl ketone with ethyl succinate under the influence of alcoholic sodium ethoxide. Depending on the conditions of condensation, two isomeric products were isolated, ethyl hydrogen cis- $\gamma$ -phenyl- $\gamma$ -(2-furyl)itaconate (I; R = Et) and the trans-isomer (II; R = Et).



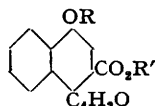
Hydrolysis of these products yielded cis- and trans- $\gamma$ -phenyl- $\gamma$ -(2-furyl)itaconic acids (I and II; R = H). On reduction with sodium amalgam the acids yielded what are believed to be the isomeric forms of  $\gamma$ -phenyl- $\gamma$ -(2-furyl)pyroracemic acid (III). This acid contains two asymmetric carbon atoms and can give two racemates.

The analysis of the acids indicates in both cases the presence of water of crystallisation, which is difficult to remove. The addition of elements of water to the furan ring during reduction, leading to an aldehyde, is unlikely, as the acids exhibit no reducing properties. No ring closures have been attempted with (III).

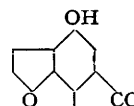
The ethyl hydrogen esters (I) and (II) were readily cyclised by acetic anhydride-sodium acetate, the cis-ester giving ethyl 4-acetoxy-7-phenylcoumarone-6-carboxylate (IV; R = Ac, R' = Et) and the trans-ester giving ethyl 1-acetoxy-4-(2'-furyl)naphthalene-3-carboxylate (V; R = Ac; R' = Et).



(IV.)



(V.)



(VI.)

The identity of the ethyl hydrogen esters and their cyclisation products was shown by oxidation of (IV) and (V) with permanganate; the former gave an almost theoretical yield of benzoic acid, but the latter gave no identifiable product.

(IV) and (V) gave on mild hydrolysis ethyl 4-hydroxy-7-phenylcoumarone-6-carboxylate (IV; R = H, R' = Et) and ethyl 1-hydroxy-4-(2'-furyl)naphthalene-3-carboxylate (V; R = H, R' = Et) respectively. Further hydrolysis yielded 4-hydroxy-7-phenylcoumarone-6-carboxylic acid (IV; R = R' = H) and 1-hydroxy-4-(2'-furyl)naphthalene-3-carboxylic acid (V; R = R' = H). The acids were characterised by their acetyl derivatives. Both (IV) and (V) (R = H) coupled normally with diazonium salts to give red dyes.

Further cyclisation of (IV; R = R' = H) with concentrated sulphuric acid gave 2-hydroxy-9-keto-3':2':3:4-furofluorene (VI), purified and obtained crystalline through its acetyl derivative.

• Patent pending.

Alternatively (IV; R = Ac, R' = H) was converted into its *acid chloride* and *anhydride* and cyclised by aluminium chloride, yielding the acetyl derivative of (VI).

The sodium salt of (VI) is distinguished by its deep purple colour, corresponding to the blue sodium salt of the hydroxybenzfluorenone of Borsche (*loc. cit.*). Various derivatives of (VI) were formed, including the acetate, the *benzoate*, and the *methyl ether*, and its *oxime*. (VI) functioned as a colour coupler in photographic developers, forming with the oxidation product of dialkyl-*p*-phenylenediamines a warm brown dye image (patent pending).

Attempts further to cyclise (V; R' = H) gave no crystalline products.

From the *cis*-phenylfurylitaconic acid (I; R = H) a good yield of 1-*keto*-3-(2'-*furyl*)*indene*-2-*acetic acid* was obtained on cyclisation with cold concentrated sulphuric acid. It was characterised by its 2 : 4-*dinitrophenylhydrazone*, and on refluxing with acetic anhydride-sodium acetate gave an excellent yield of the acetyl derivative of (VI).

The *trans*-phenylfurylitaconic acid could not be cyclised.

#### EXPERIMENTAL.

Analyses are by Drs. Weiler and Strauss, Oxford. M. p.'s are corrected. The majority of the compounds have a softening-melting range rather than a sharp m. p., even after repeated crystallisation.

Phenyl furyl ketone, prepared according to Marquis (*Ann. Chim. Phys.*, 1905, 4, 276) from furoyl chloride, distilled at 285°/760 mm.

*Ethyl Hydrogen cis-γ-Phenyl-γ-(2-furyl)itaconate* (I; R = Et).—A mixture of phenyl furyl ketone (68.8 g.; 0.4 mol.) and ethyl succinate (66.7 c.c.; 0.4 mol.) was added in a thin stream, with shaking, to a warm solution of sodium ethoxide (18.4 g.; 0.8 mol. of sodium) in absolute alcohol; it turned red and partly gelled. The whole was heated on the water-bath for ½ hour, and water then added until no more oil was precipitated. The oil, consisting of neutral components, was removed in ether, and the alkaline solution acidified. The oil thus precipitated was dissolved in ether and dried (sodium sulphate), and the ether removed. The yellow-brown oil slowly formed a mass of oil-soaked crystals. These were separated from the oil (40 g.; not further examined) by filtration and washed with a little ether (yield, 40 g.; 33% of the theoretical). Recrystallised from aqueous acetone, they gave lustrous flat needles, m. p. 154—156° after softening at 149° (Found : C, 68.0; H, 5.4. C<sub>17</sub>H<sub>16</sub>O<sub>5</sub> requires C, 68.0; H, 5.4%). With concentrated sulphuric acid a blood-red solution was formed.

*Ethyl Hydrogen trans-γ-Phenyl-γ-(2-furyl)itaconate* (II; R = Et).—A mixture of phenyl furyl ketone (100 g.; 0.58 mol.) and ethyl succinate (95 c.c.; 0.58 mol.) was shaken at room temperature with a solution of sodium ethoxide (26.5 g.; 1.16 mols. of sodium) in an excess of absolute alcohol. After 12 hours, the whole was heated on the water-bath for 15 minutes, and water added. The precipitated neutral oil was removed in ether, and the alkaline solution neutralised with dilute hydrochloric acid. The oil thus precipitated solidified completely (yield, 109 g.). (If the alkaline solution was acidified, the oil only partly solidified, possibly owing to precipitation of an oily by-product by the excess of acid.) The cake was broken up, dried in a vacuum, and dissolved in methylene chloride, and ligroin gradually added. The first crop of crystals (10 g.) consisted of the ethyl hydrogen *cis*-ester, m. p. 154—156°, and the second crop (70 g.), m. p. 93—96°, of the *trans*-form (27.5%). Recrystallised from benzene-ligroin, the *ethyl hydrogen trans-ester* formed light fawn needle clusters, m. p. 93—96° (Found : C, 68.2; H, 5.4%). With concentrated sulphuric acid a blood-red solution was formed.

*cis-γ-Phenyl-γ-(2-furyl)itaconic Acid* (I; R = H).—A solution of the ethyl hydrogen *cis*-ester (5 g.) in 2.5% aqueous potassium hydroxide (200 c.c.) was boiled for 1 hour, acidified while hot, and allowed to cool. The crystals obtained were recrystallised from methanol-hot water, the *cis-acid* forming colourless prisms (4 g.), m. p. 208—215° (decomp.) (Found : C, 65.9; H, 4.5. C<sub>15</sub>H<sub>12</sub>O<sub>5</sub> requires C, 66.1; H, 4.5%).

*trans-γ-Phenyl-γ-(2-furyl)itaconic Acid* (II; R = H).—The ethyl hydrogen *trans*-ester was treated similarly. Acidification produced a yellow oil, which slowly crystallised. From benzene, the *trans-acid* formed fawn prisms (4.1 g.), m. p. 148—154° (Found : C, 66.4; H, 4.5%).

*Reduction of cis- and trans-Phenylfurylitaconic Acids : γ-Phenyl-γ-(2-furyl)pyroracemic Acids* (III).—10% Sodium amalgam (30 g.) was added during 6 hours to a solution of the acid (0.2 g.) in 10% aqueous sodium hydroxide (100 c.c.) heated on the water-bath, carbon dioxide being passed over the surface. The solution was decanted, the mercury washed, and the combined aqueous solutions filtered and acidified. From both acids, bulky white precipitates were obtained, which were washed with water and recrystallised from hot water.

The *pyroracemic acid* formed from the *cis*-itaconic acid formed balls of fine silky needles, m. p. 93—98°, and that from the *trans*-itaconic acid formed long silky needles, m. p. 103—108°. The mixed m. p. was never lower than 93—98°. Both acids contained one molecule of water of crystallisation (Found : for acid of m. p. 93—98°, C, 61.6; H, 5.5; for acid of m. p. 103—108°, C, 62.0; H, 5.6. C<sub>15</sub>H<sub>14</sub>O<sub>5</sub>.H<sub>2</sub>O requires C, 61.6; H, 5.5%).

*Ring Closures with Ethyl Hydrogen cis-Phenylfurylitaconate* (I; R = Et).—(a) *With sulphuric acid*. The ester (0.5 g.) was dissolved in ice-cold concentrated sulphuric acid (10 c.c.), and the deep red solution kept at 4° for 20 hours and poured into water; red flocks formed which could not be crystallised. They gave a dirty brown dinitrophenylhydrazone, which also could not be obtained crystalline.

(b) *With acetic anhydride*. A mixture of the ester (61.0 g.), anhydrous sodium acetate (40 g.), and acetic anhydride (210 c.c.) was boiled for 3 hours, the yellow liquor concentrated in a vacuum, and the remaining anhydride decomposed with water. The yellow oil slowly crystallised. The yield of crude *ethyl 4-acetoxy-7-phenylcoumarone-6-carboxylate* (IV; R = Ac, R' = Et) was almost theoretical. Recrystallised from methanol, it formed white crystal aggregates, m. p. 105—108°. It fluoresced blue in ultra-violet light (Found : C, 70.3; H, 4.9. C<sub>17</sub>H<sub>16</sub>O<sub>5</sub> requires C, 70.35; H, 5.0%).

*Ethyl 4-hydroxy-7-phenylcoumarone-6-carboxylate* (IV; R = H, R' = Et) was readily obtained on acidification of the solution obtained by dissolving the acetoxy-derivative in spirit and adding an excess of warm 5% aqueous sodium hydroxide. From hot dilute acetic acid, it formed colourless needles, m. p. 178—181°; these absorbed ultra-violet light strongly (Found : C, 71.85; H, 5.1. C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> requires C, 72.3; H, 5.0%).

*4-Hydroxy-7-phenylcoumarone-6-carboxylic Acid* (IV; R = R' = H).—The crude acetoxy-ester (4.5 g.) was dissolved in spirit (10 c.c.) and boiled for 2 hours with 4% aqueous potassium hydroxide (50 c.c.). The solution was concentrated to half its volume in a vacuum, diluted to 100 c.c. with water, and acidified while hot. The yellow oil obtained soon solidified. From dilute acetic acid, it formed buff-coloured flat needles, m. p. 214—217°, containing ½ mol. of water of crystallisation, removable by heating above 110° for 3 hours (Found : C, 68.6; H, 4.15. C<sub>15</sub>H<sub>10</sub>O<sub>4</sub>.½H<sub>2</sub>O requires C, 68.4; H, 4.2%). The red dye obtained by coupling with diazotised aniline formed red spears, m. p. 230—236° (decomp.), from chloroform.

4-Acetoxy-7-phenylcoumarone-6-carboxylic acid (IV; R = Ac, R' = H) was formed on warming (IV; R = R' = H) with acetic anhydride and sodium acetate for 5 minutes on the water-bath. It crystallised from methanol in colourless prisms which effloresced, releasing methanol of crystallisation. Dried at 100°/20 mm. for 2 hours, it formed a colourless powder, m. p. 236—238° (Found: C, 68.8; H, 4.15. C<sub>17</sub>H<sub>13</sub>O<sub>5</sub> requires C, 68.9; H, 4.1%).

*Ring Closure of 4-Hydroxy-7-phenylcoumarone-6-carboxylic Acid.*—The coumarone (5 g.) was dissolved in ice-cold concentrated sulphuric acid (100 c.c.) and after 15 minutes the green solution was poured into ice-water, and the flocculent brick-red precipitate collected and washed. The crude fluorenone could not be crystallised, so it was acetylated by solution in hot acetic anhydride and sodium acetate, giving, on recrystallisation from methanol, golden needles of 9-keto-2-acetoxy-3':2':3:4-furofluorene, m. p. 169—171° (Found: C, 73.5; H, 3.7. C<sub>17</sub>H<sub>10</sub>O<sub>4</sub> requires C, 73.4; H, 3.6%). The 2:4-dinitrophenylhydrazones formed orange needles, m. p. 278—280°, from chloroform (Found: N, 12.45. C<sub>23</sub>H<sub>14</sub>O<sub>7</sub>N<sub>4</sub> requires N, 12.2%).

When an alcoholic solution of the acetoxy-derivative was warmed with an excess of sodium hydroxide, the yellow solution became deep purple. It was neutralised, and the red precipitate collected and crystallised from glacial acetic acid, forming blood-red plates, m. p. 221—227°, of 2-hydroxy-9-keto-3':2':3:4-furofluorene (VI) (Found: C, 76.8; H, 3.7. C<sub>18</sub>H<sub>12</sub>O<sub>5</sub> requires C, 76.2; H, 3.4%). The sodium salt formed purple needles or spears.

*Ring Closure of 4-Acetoxy-7-phenylcoumarone-6-carboxylic Acid: 9-Keto-2-acetoxy-3':2':3:4-furofluorene.*—(a) *With aluminium chloride and the acid chloride.* The acetoxy-derivative (2 g.) was covered with thionyl chloride (10 c.c.) and warmed, hydrogen chloride being briskly evolved. The excess of thionyl chloride was distilled, and the residue, which soon solidified to a yellow crystalline cake, recrystallised from benzene. The acid chloride formed colourless needles, m. p. 157—160° (Found: Cl, 11.3. C<sub>17</sub>H<sub>11</sub>O<sub>4</sub>Cl requires Cl, 11.3%). It was dissolved in carbon disulphide (20 c.c.), aluminium chloride (2 g.) added, and the mixture warmed for 1 hour on the water-bath. The carbon disulphide was driven off, and the black residue decomposed with dilute hydrochloric acid. The yellow flocks (1.2 g.) crystallised from methanol in yellow needles, m. p. 169°, identical with the acetyl derivative of (VI) obtained from the sulphuric acid cyclisation product.

(b) *With aluminium chloride and the anhydride.* The acetylated acid (2 g.) and acetyl chloride (15 c.c.) were warmed until evolution of hydrogen chloride ceased; the excess of solvent was then removed in a vacuum, leaving an oil which soon crystallised. Recrystallised from benzene, the anhydride formed colourless plates, m. p. 110—114° (Found: C, 70.9; H, 3.8. C<sub>34</sub>H<sub>22</sub>O<sub>5</sub> requires C, 71.1; H, 3.9%). The crude anhydride, treated as in the case of the acid chloride, yielded the desired acetoxy-compound (1.3 g.), m. p. 170°.

The benzoate formed canary-yellow needles, m. p. 183—184°, from benzene (Found: C, 77.5; H, 3.5. C<sub>22</sub>H<sub>12</sub>O<sub>4</sub> requires C, 77.6; H, 3.6%). The methyl ether formed fine orange needles, m. p. 159—160°, from methanol (Found: C, 76.75; H, 4.1. C<sub>16</sub>H<sub>10</sub>O<sub>3</sub> requires C, 76.8; H, 4.0%), and its oxime canary-yellow needles, m. p. 233—234°, from methanol (Found: N, 5.25. C<sub>16</sub>H<sub>11</sub>O<sub>3</sub>N requires N, 5.3%).

*Ring Closure of cis-γ-Phenyl-γ-(2-furyl)itaconic Acid (I; R = H).*—(a) With acetic anhydride and sodium acetate a brown oil was obtained which could not be crystallised.

(b) *With sulphuric acid.* The cis-acid (0.54 g.), added slowly to concentrated sulphuric acid (15 c.c.) at 25°, dissolved to a deep green solution. After 15 minutes this was poured into ice-water, and the precipitate collected, washed with water, and recrystallised from acetic acid, giving brick-red needles (0.4 g.), m. p. 192—197°, of 1-keto-3-(2'-furyl)indene-2-acetic acid (Found: C, 70.4; H, 4.0. C<sub>16</sub>H<sub>10</sub>O<sub>4</sub> requires C, 70.8; H, 4.0%). The 2:4-dinitrophenylhydrazones, recrystallised from alcohol, had m. p. 215—217° (Found: N, 12.75. C<sub>21</sub>H<sub>14</sub>O<sub>7</sub>N<sub>4</sub> requires N, 12.9%).

The indoneacetic acid (0.8 g.) was boiled for 1½ hours with acetic anhydride (5 c.c.) and anhydrous sodium acetate (0.5 g.). After destruction of the acetic anhydride 0.8 g. of 9-keto-2-acetoxy-3':2':3:4-furofluorene, m. p. 170°, was obtained.

*Cyclisation of Ethyl Hydrogen trans-γ-Phenyl-γ-(2-furyl)itaconate: Ethyl 1-Acetoxy-4-(2'-furyl)naphthalene-3-carboxylate (V; R = Ac, R' = Et).*—The ethyl hydrogen trans-ester (61 g.), anhydrous sodium acetate (40 g.), and acetic anhydride (210 c.c.) were boiled for 3 hours, most of the anhydride removed in a vacuum, and the rest poured into water. The dark brown oil solidified. Recrystallised from isopropyl ether-ligroin or methanol, the substance formed fawn leaflets (55 g.), m. p. 78—81° (Found: C, 70.2; H, 4.9. C<sub>19</sub>H<sub>16</sub>O<sub>5</sub> requires C, 70.35; H, 5.0%).

*Ethyl 1-hydroxy-4-(2'-furyl)naphthalene-3-carboxylate (V; R = H, R' = Et)* was readily formed by warming an alcoholic solution of the 1-acetoxy-derivative with 10% aqueous potassium hydroxide and acidifying the product. Recrystallised from dilute acetic acid, the substance formed fawn needles, m. p. 151—153° (Found: C, 71.9; H, 4.9. C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> requires C, 72.3; H, 5.0%).

*1-Hydroxy-4-(2'-furyl)naphthalene-3-carboxylic Acid (V; R = R' = H).*—The ethyl ester (5 g.), dissolved in spirit (25 c.c.), was boiled with 5% aqueous potassium hydroxide (100 c.c.) for 2 hours. After filtration and neutralisation the acid was recrystallised from methanol-hot water (Found: C, 70.6; H, 4.2. C<sub>15</sub>H<sub>10</sub>O<sub>4</sub> requires C, 70.8; H, 4.0%). It coupled with diazotised aniline, giving a red dye, reduced silver nitrate, and gave with concentrated sulphuric acid a red coloration.

*1-Acetoxy-4-(2'-furyl)naphthalene-3-carboxylic acid (V; R = Ac, R' = H),* obtained on acetylating the above acid, recrystallised from acetone-ligroin in fine needles, m. p. 154—156° (Found: C, 68.65; H, 4.2. C<sub>17</sub>H<sub>12</sub>O<sub>5</sub> requires C, 68.9; H, 4.1%).