[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

β-Duroylphenylpropionic Acids

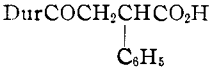
BY REYNOLD C. FUSON AND ROBERT G. BANNISTER[1]

β-Duroyl-α-phenylpropionic and β-duroyl-β-phenylpropionic acids have been prepared by unequivocal methods. Dehydration of the acids by the action of acetyl chloride produced lactones.

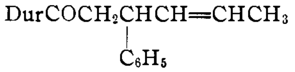
Oxidation of the product (II) obtained by condensing phenylmagnesium bromide with sorbodurene (I) yielded a keto acid which was believed to be β-duroyl-α-phenylpropionic acid (III).[2]

$\mathrm{DurCOCH{=}CHCH{=}CHCH_3}$

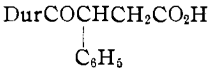
I


$\mathrm{DurCOCH_2\underset{C_6H_5}{CH}CO_2H}$

III


$\mathrm{DurCOCH_2\underset{C_6H_5}{CH}CH{=}CHCH_3}$

II


$\mathrm{DurCO\underset{C_6H_5}{CH}CH_2CO_2H}$

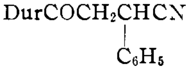
IV

Confirmation of this structure has been obtained by synthesis of the keto acid and its isomer, β-duroyl-β-phenylpropionic acid (IV), by independent methods.

The α-phenyl acid (III) was prepared by hydrolysis of the corresponding nitrile (VI), a condensation product of benzalacetodurene (V) with hydrogen cyanide. The nitrile was obtained in nearly quantitative yields, but its hydrolysis afforded the desired acid in yields of only 30%.

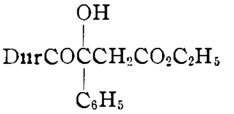
$\mathrm{DurCOCH{=}CHC_6H_5}$

V

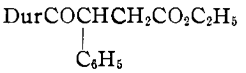

$\mathrm{DurCOCH_2\underset{C_6H_5}{CH}CN}$

VI

An unequivocal synthesis of the β-phenyl acid (IV) involved the condensation of ethyl bromoacetate with duryl phenyl diketone by the Reformatsky method. Dehydration of the hydroxy ester (VII), difficult to effect, was finally achieved by a mixture of thionyl chloride and pyridine. Hydrogenation of the resulting unsaturated ester yielded the ethyl ester (VIII) of the desired acid.


$\mathrm{DurCO\overset{OH}{\underset{C_6H_5}{C}}CH_2CO_2C_2H_5}$

VII

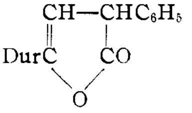

$\mathrm{DurCO\underset{C_6H_5}{CH}CH_2CO_2C_2H_5}$

VIII

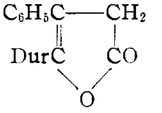
It was found later that the saturated ester (VIII) could be prepared directly and much more satisfactorily by treating the hydroxy ester with a solution of hydrogen iodide in a mixture of glacial acetic acid and acetic anhydride. Hydrolysis of the ester (VIII) furnished the β-phenyl acid (IV). Another route to this acid involved the condensation of ethyl bromoacetate with benzyl duryl ketone in the presence of sodium ethoxide. The yield of acid obtained by this procedure was very low.

The condensation of durene with phenylsuccinic anhydride produced a mixture of the α- and β-phenylated β-duroylpropionic acids. The total yield of the mixture of acids was 41% of the theoretical. Separation of the mixture afforded the pure α-phenyl acid (III) in 6.7% yield and the pure β-phenyl acid (IV) in a yield of 14.4%.

With acetyl chloride the α-phenyl acid yielded a lactone to which was assigned structure IX by analogy to that obtained from α-phenyl-β-mesitoylpropionic acid.[3] A similar treatment of the β-phenyl acid converted it to a lactone (X) also.



IX



X

Both lactones are opened by alkali, and the original acids may be regained by acidification of the alkaline solutions.

Experimental

Benzalacetodurene.—A mixture of 75 g. of acetodurene, 53 ml. of benzaldehyde, 150 ml. of ethanol and 50 ml. of 10% sodium hydroxide solution was allowed to stand overnight. The crystalline benzalacetodurene was isolated by filtration. An additional amount of product was obtained by concentration of the mother liquor, the total yield being 87.3 g. (78%). The ketone crystallized from ethanol in needles having a faint green color; m.p. 95°.

Anal.[4] Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.07; H, 7.69.

β-Duroyl-α-phenylpropionitrile (VI).—A solution of 65 g. of potassium cyanide in 150 ml. of water was added dropwise over a period of one hour to a solution of 106.5 g. of benzalacetodurene, 1350 ml. of 95% ethanol and 31 ml. of glacial acetic acid. The reaction mixture was stirred continuously and maintained at 35° during the addition. When allowed to stand for an hour the mixture solidified. After standing in the ice-box for 24 hours it was filtered. By concentration of the mother liquor an additional amount of product was obtained; yield 113 g. After being recrystallized three times from ethanol the nitrile formed white, silky needles; m.p. 117–117.5°.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.48; H, 7.40; N, 4.99.

β-Duroyl-α-phenylpropionic Acid (III).—A mixture of 95 g. of β-duroyl-α-phenylpropionitrile, 300 ml. of glacial acetic acid, 200 ml. of concentrated sulfuric acid and 200 ml. of water was heated under reflux overnight. Water was added and the solution allowed to cool; the acid separated as an oily layer which crystallized. It was recrystallized from nitromethane; yield 30.6 g. (30.4%). After being recrystallized twice from ethyl acetate, the white prisms melted at 185–185.5°.

The acid was prepared in 25.8% yield by base-catalyzed hydrolysis. A mixture of 25.8 g. of the nitrile, 100 ml. of ethanol, 25 g. of potassium hydroxide and 50 ml. of water was boiled under reflux for 2 days and acidified. The acid, recrystallized from ethyl acetate, melted at 185–185.5°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; neut. equiv., 310. Found: C, 77.21; H, 6.96; neut. equiv., 313.

Mixtures of the two samples of the acid with one another and with that prepared earlier[2] showed no depression of the melting point.

---

[1] Atomic Energy Commission Fellow, 1949–1950.

[2] R. C. Fuson and W. H. Libby, *J. Org. Chem.*, **16**, 626 (1951).

[3] C. F. H. Allen, J. B. Normington and C. V. Wilson, *Can. J. Res.*, **11**, 382 (1934).

[4] Microanalyses by Miss Emily Davis, Mrs. Jean Fortney and Miss Rachel Kopel.

Lactone formation occurred when a solution of the acid (III) in acetyl chloride was allowed to evaporate in a vacuum desiccator. The product was partially soluble in boiling methylcyclohexane, the solution being deep red at the boiling point. When the solution was cooled the color faded to a faint pink. The lactone (0.5 g.) crystallized from methylcyclohexane in clusters of white needles; m.p. 179.5–180°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.00; H, 7.11.

The material which was insoluble in methylcyclohexane (2 g.) was recrystallized from toluene; m.p. 227–228°, with decomposition. *Anal.* Found: C, 78.61; H, 6.93.

This compound was not identified.

A solution of the lactone (3 g.), 15 ml. of dioxane, 1 g. of potassium hydroxide and 25 ml. of water yielded the original acid when acidified.

An attempt to prepare a *p*-chlorobenzal derivative of this lactone failed, the only product being the high-melting (227–228°) substance obtained in the lactonization procedure.

Methyl β-Duroyl-α-phenylpropionate.—β-Duroyl-α-phenylpropionic acid (14.7 g.) was added to 300 ml. of methanol saturated with dry hydrogen chloride, and the mixture boiled under reflux overnight. The crude ester (13.1 g.) was crystallized from methanol; m.p. 81–81.5°.

Anal. Calcd. for $C_{21}H_{24}O_3$; C, 77.75; H, 7.64. Found: C, 77.66; H, 7.54.

α-Bromoacetodurene.—A possible route to the α-phenyl acid (III) involved condensation of α-bromoacetodurene with phenylacetonitrile. The synthesis failed at the first step. Bromoacetyl chloride, made by the action of thionyl chloride on 97.5 g. of bromoacetic acid, was mixed with 1 l. of carbon disulfide and 94.9 g. of durene. Anhydrous aluminum chloride (120 g.) was added gradually to the solution over a period of one hour. The α-bromoacetodurene was isolated with difficulty; 65.3 g. (36.5%) was obtained in crystalline form. When recrystallized three times from ethanol it formed white needles; m.p. 53–54°.

Anal. Calcd. for $C_{12}H_{15}OBr$: C, 56.48; H, 5.93. Found: C, 56.71; H, 6.08.

The compound had a faint odor and was irritating to the nose and skin. An attempt to condense it with phenylacetonitrile in the presence of sodium ethoxide gave only tarry products.

Ethyl β-Duroyl-β-hydroxy-β-phenylpropionate (VII).—To 50 g. of activated zinc[5] was added a small amount of a solution of 93.2 g. of duryl phenyl diketone in 80 g. of ethyl bromoacetate and 100 ml. of dry benzene; a few crystals of mercuric chloride were added and heat was used to initiate the reaction. As soon as the reaction had begun, the remainder of the ester solution was added at such a rate that the mixture continued to boil. After all the solution had been added, boiling under reflux was maintained for one hour. The mixture was allowed to cool and was poured into 500 ml. of cold 10% sulfuric acid. The crude ester was recrystallized from ethanol; yield 83.4 g. (67.2%); m.p. 109–111°. After being recrystallized three more times from ethanol, the white rhombic platelets melted at 111.5–112.5°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.76; H, 7.38.

The infrared spectrum[6] of the compound contained bands at 1691, 1703 and 3448 cm.$^{-1}$, which correspond, respectively, to the ketone, ester and hydroxyl functions.

β-Duroyl-β-hydroxyl-β-phenylpropionic Acid.—A mixture of 2.5 g. of the ester (VII), 5 g. of potassium hydroxide, 100 ml. of ethanol and 40 ml. of water was heated under reflux overnight. The acid, recrystallized twice from nitromethane and once from a mixture of benzene and high-boiling petroleum ether, formed white prisms; m.p. 158–159°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; neut. equiv., 326. Found: C, 73.49; H, 6.97; neut. equiv., 331.

Ethyl β-Duroyl-β-phenylacrylate.—A solution of 50 g. of β-duroyl-β-hydroxy-β-phenylpropionate in 35 ml. of pyridine and 100 ml. of dry benzene was cooled in an ice-bath and 15 ml. of thionyl chloride was added. The mixture was boiled gently under reflux (air condenser) overnight and treated with dilute hydrochloric acid. The crude unsaturated ester crystallized from ethanol (46.6%). After being recrystallized two more times it formed faintly yellowish-green needles; m.p. 128–129°.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.40; H, 7.15.

The infrared spectrum contained strong bands at 1675 and 1735 cm.$^{-1}$ and a weak band at 1631 cm.$^{-1}$; these bands correspond to ketone, ester and olefinic functions, respectively.

Methyl β-Duroyl-β-phenylacrylate.—A solution of the ethyl ester (3 g.) in 50 ml. of methanol, previously saturated with dry hydrogen chloride, was heated under reflux for 8 hours. The methyl ester, after being recrystallized three times from methanol, formed yellowish-green needles; m.p. 124.5–125°.

Anal. Calcd. for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.07; H, 6.86.

Ethyl β-Duroyl-β-phenylpropionate (VIII).—To a solution of 10 g. of the unsaturated ester in 200 ml. of ethyl acetate was added 0.3 g. of Adams platinum oxide catalyst and the solution was exposed to an atmosphere of hydrogen at 50 lb. per sq. in. on a shaking machine. The saturated ester crystallized from low-boiling petroleum ether in white needles; m.p. 84–85.5°.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.17; H, 7.61.

The infrared spectrum contained bands at 1687 and 1735 cm.$^{-1}$, which correspond, respectively, to the ketone and ester functions.

α-Bromobenzyl Duryl Ketone.—An attempt was made to proceed to the α-phenyl acid by alkylation of ethyl malonate with α-bromobenzyl duryl ketone. To a solution of ethylmagnesium bromide, prepared from 13 g. of ethyl bromide and 4.5 g. of magnesium in dry ether, was added a solution of 28.6 g. of benzyl duryl ketone in dry ether. A solution of 10 g. of bromine in ether was added to the mixture dropwise. The crude bromo ketone (23.2 g.) was recrystallized from ethanol. It formed white needles; m.p. 98.5–99°.

Anal. Calcd. for $C_{18}H_{19}OBr$: C, 65.26; H, 5.78. Found: C, 65.38; H, 5.82.

The bromo ketone was treated with ethyl malonate in the presence of sodium ethoxide and the product saponified with potassium hydroxide solution. The only crystalline product which could be isolated melted, after recrystallization successively from nitromethane and ethyl acetate, at 176–177°. It was not identified.

Anal. Found: C, 73.95; H, 8.15.

β-Duroyl-β-phenylpropionic Acid (IV).—A solution of 7 g. of ethyl β-duroyl-β-phenylpropionate, 100 ml. of ethanol, 5 g. of potassium hydroxide and 50 ml. of water was heated under reflux for 8 hours. The acid was isolated by conventional methods.

The same acid was obtained directly by heating for 2 hours under reflux a solution of ethyl β-duroyl-β-hydroxy-β-phenylpropionate (18 g.), a crystal of iodine, 200 ml. of glacial acetic acid, 200 ml. of acetic anhydride and 200 ml. of 47% hydriodic acid solution. The acid crystallized from ethyl acetate in white prisms; m.p. 185–184.5°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; neut. equiv., 310. Found: C, 77.51; H, 7.38; neut. equiv., 312.

The infrared spectrum of a solution of the acid in dioxane contained bands at 1700 and 1736 cm.$^{-1}$, corresponding to ketone and carboxyl groups, respectively. A melting point depression was observed when this acid was mixed with the acid obtained from α-bromobenzyl duryl ketone (m.p. 176–177°) or with β-duroyl-α-phenylpropionic acid (m.p. 185–185.5°).

β-Duroyl-β-phenylpropionic Acid (IV). Second Method. Benzyl duryl ketone when heated for 30 hours with ethyl bromoacetate in the presence of sodium ethoxide gave a small amount of white prisms melting at 182–183°.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 76.75; H, 6.92.

A mixture of this compound with β-duroyl-β-phenylpro-

---

[5] L. F. Fieser and W. S. Johnson, THIS JOURNAL, **62**, 575 (1940).

[6] The infrared absorption spectra were observed and interpreted by Miss Elizabeth Petersen.

pionic acid described earlier showed no depression in melting point.

Lactone formation was effected by allowing a solution of 3.9 g. of the keto acid (IV) in acetyl chloride to stand in a vacuum desiccator. After three recrystallizations from methylcyclohexane the lactone formed white, silky needles (3.1 g.); m.p. 142°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.22; H, 7.12.

The lactone sublimed without change at 165–175° (0.01 mm.). The infrared spectrum contained bands at 1656 and 1801 cm.$^{-1}$, which correspond to the olefinic and lactone functions, respectively.

The lactone (1 g.) was dissolved in a mixture of 20 ml. of dioxane, 50 ml. of water and 2 g. of potassium hydroxide; acidification of this mixture produced β-duroyl-β-phenylpropionic acid (0.7 g.).

To a benzene solution of 1 g. of the lactone and 0.5 g. of *p*-chlorobenzaldehyde was added a few drops of diethylamine and the mixture was heated under reflux for 30 minutes, additional quantities of amine being added from time to time. The ***p*-chlorobenzal derivative** (0.3 g.) separated from methylcyclohexane in yellow crystals; m.p. 204–205°.

Anal. Calcd. for $C_{27}H_{23}O_2Cl$; C, 78.15; H, 5.59. Found: C, 78.29; H, 5.70.

Methyl β-Duroyl-β-phenylpropionate.—A solution of the acid (3 g.) in methanol, previously saturated with hydrogen chloride, was heated under reflux for 8 hours. The methyl ester was recrystallized three times from methanol; m.p. 88–89°.

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.51; H, 7.68.

Condensation of Phenylsuccinic Anhydride with Durene.—A mixture of 30 g. of phenylsuccinic anhydride, 22 g. of durene, 50 g. of anhydrous aluminum chloride and 300 ml. of carbon disulfide was heated for a few minutes in order to break up the lumps formed initially. After a reaction time of 3 hours the mixture was poured on ice. Hydrochloric acid was added and the carbon disulfide distilled. A solution of the mixture of acids in 95% ethanol was boiled with Darco and filtered. The yield of crystalline material from the fitrate was 21.4 g. (41%). A solution of the product in ethyl acetate was seeded alternately with the α- (III) and β-phenyl (IV) derivatives of β-duroylpropionic acid. Successful separation was achieved only when 0.5–1.0 g. was removed at a time. Very little of the α-phenyl acid could be recovered from ethyl acetate solution; however, nitromethane proved to be a good solvent for the isolation of this acid. By recrystallizing the acids twice from ethyl acetate it was possible to obtain 7.6 g. of the pure β-phenyl acid and 3.5 g. of the pure α-phenyl acid. Mixture melting points with authentic samples were taken as criteria of identity. At the end of this procedure 5.0 g. of crystalline residue remained; m.p. 161–165°. It was not identified.

URBANA, ILLINOIS RECEIVED OCTOBER 11, 1951

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Conjugate Addition of Hydrogen Cyanide to β-Mesityl Ketones

BY REYNOLD C. FUSON AND ROBERT G. BANNISTER[1]

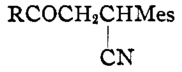
Hydrogen cyanide condenses in the conjugate manner with mesitalacetomesitylene, mesitalacetophenone and mesitalacetone, producing the corresponding keto nitriles in high yields.

It has been established that a mesityl radical in the β-position in an α,β-unsaturated carbonyl compound does not block entry by the hydrocarbon radical of a Grignard reagent at that position even when the reagent is mesitylmagnesium bromide. Attack at the β-position can occur whether the carbonyl group itself is hindered[2,3] or not.[4] It remains to be shown whether other reagents, less active toward the carbonyl function than Grignard reagents, are capable of conjugate addition to such systems. In the present work it has been found that hydrogen cyanide can be added in the conjugate manner to α,β-unsaturated carbonyl compounds in which the β-carbon atom holds a mesityl radical.

Mesitalacetomesitylene (I) combines with hydrogen cyanide to give the expected keto nitrile (III) in high yield.[5]

RCOCH=CHMes

I, R = Mes
II, R = C_6H_5



$$RCOCH_2\underset{\displaystyle CN}{\underset{|}{C}}HMes$$

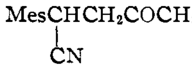
III, R = Mes
IV, R = C_6H_5

Similarly mesitalacetophenone (II) is converted to the unhindered keto nitrile, IV. Both compounds therefore behave toward hydrogen cyanide as typical chalcones.

Mesitalacetone (V) is interesting since it is a vinylog of acetomesitylene, a ketone which does not combine with hydrogen cyanide. As a methyl ketone mesitalacetone should be capable of yielding a cyanohydrin. Moreover, the mesityl group in the β-position might be expected to oppose conjugate addition. This ketone, however, was found to combine with hydrogen cyanide at 35° to give, in 63% yield, the keto nitrile (VI) corresponding to conjugate addition. No other product could be isolated.

MesCH=CHCOCH$_3$

V



$$Mes\underset{\displaystyle CN}{\underset{|}{C}}HCH_2COCH_3$$

VI

A related reaction, employed in the preparation of mesitylsuccinic acid (IX), involves conjugate addition of hydrogen cyanide to ethyl mesitalmalonate (VII). The yield of acid was low but, since the cyano ester (VIII) was not isolated, it is not possible to say whether the conjugate addition took place readily.

---

[1] Atomic Energy Commission Fellow, 1949–1951.

[2] E. P. Kohler and L. W. Blanchard, Jr., THIS JOURNAL, **57**, 367 (1935).

[3] R. C. Fuson and J. S. Meek, *J. Org. Chem.*, **10**, 551 (1945).

[4] R. C. Fuson and H. L. Jackson, THIS JOURNAL, **72**, 1637 (1950).

[5] It was pointed out by a Referee that the *cis* configuration for I is virtually impossible as a coplanar system, requiring nearly 90° distortion. Perpendicular attack at the olefinic bond is thus inhibited. The high yield of III accordingly requires that I have the *trans* configuration, assuming of course that the addition is initiated by attack of cyanide ion.

Attention was also called to the fact that the infrared absorption band attributable to the carbonyl function of III falls between that for the unconjugated carbonyl of VI and the "normal" aromatic carbonyl group of IV. This relationship may be taken as supporting evidence for the idea that the carbonyl joined to the mesityl radical is somewhat out of the plane of the mesityl ring and hence less highly conjugated.