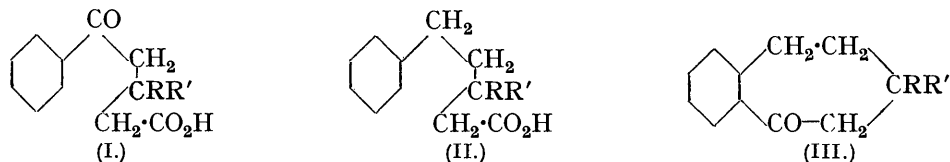


213. *The Friedel–Crafts Condensation of Substituted Glutaric Anhydrides with Benzene and the Formation of Isomeric Benzoylphenylpropionic Acids in the Reaction between Phenylsuccinic Anhydride and Benzene.*

By AHMED ALI, R. D. DESAI, R. F. HUNTER, and S. M. MAKHDHUM MUHAMMAD.

ALTHOUGH the Friedel–Crafts reaction between succinic anhydrides and aromatic hydrocarbons has been extensively studied (Oppenheim, *Ber.*, 1901, **34**, 4228; Mayer and Stamm, *Ber.*, 1923, **56**, 1424; Krollpfeiffer and Schafer, *ibid.*, p. 620; Haworth and collaborators, *J.*, 1932, 1125, 1784, 2717, and later), the corresponding reaction with derivatives of glutaric acid, with the exception of the condensation of glutaric anhydride itself with anisole and phenetole (Plant and Tomlinson, *J.*, 1935, 856), has not previously been investigated.

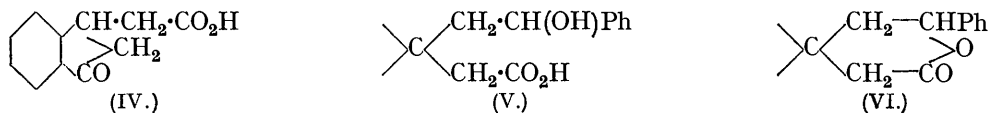
Additional interest attaches to the keto-acids (I) in that the products of their reduction by the Clemmensen method (II) would be expected to give rise to benzocycloheptane derivatives (III) on cyclisation.



The anhydrides of glutaric acid, $\beta\beta$ -dimethylglutaric acid, and β -methyl- β -ethylglutaric acid reacted readily with benzene in the presence of aluminium chloride, giving the expected γ -benzoyl-*n*-butyric acids (I: R = R' = H; R = R' = Me; R = Me, R' = Et), which yielded the corresponding δ -phenyl-*n*-valeric acids (II) on reduction. Attempts to convert the latter into ketocycloheptane derivatives by treatment with 85% sulphuric acid were unsuccessful on account of extensive sulphonation, and we have so far been unable to devise a satisfactory method of cyclisation.

β -Phenylglutaric anhydride did not condense with benzene; internal condensation to ketohydrindene-3-acetic acid (IV) (Speight, Stevenson, and Thorpe, J., 1924, 125, 2189) took place.

The anhydrides of cyclopentane-1:1-diacetic acid, 3-methylcyclopentane-1:1-diacetic acid, and cyclohexane-1:1-diacetic acid behaved similarly to the $\beta\beta$ -dialkylglutaric anhydrides, and gave rise to the corresponding keto-acids on condensation with benzene. The 1- β -phenylethyl-cyclopentane- and -cyclohexane-1-acetic acids (II: RR' = C₄H₈; RR' = C₅H₁₀) obtained by the Clemmensen method were accompanied by small amounts of neutral products, whose composition suggests that they are the lactones (VI) of the corresponding 1- β -hydroxy- β -phenylethyl-1-acetic acids (V).



By the condensation of phenylsuccinic anhydride with benzene, Anschütz, Hahn, and Walter (*Annalen*, 1907, 354, 150) obtained β -benzoyl- β -phenylpropionic acid (VII). We have found, however, that the isomeric β -benzoyl- α -phenylpropionic acid (VIII) and a high-melting neutral product, whose composition suggests that it is the lactone of γ -hydroxy- $\alpha\gamma\gamma$ -triphenyl-*n*-butyric acid (IX) or its $\beta\gamma\gamma$ -triphenyl isomer (X), are also formed.



The acid (VII) proved identical with that prepared by hydrolysis of the ester obtained from the condensation of the sodio-derivative of deoxybenzoin with ethyl bromoacetate. β -Benzoyl- α -phenylpropionic acid (VIII) was also synthesised for comparison, but in poor yield, by hydrolysis of the product of condensation of ω -bromoacetophenone and phenylacetonitrile in the presence of sodium ethoxide (compare Lapworth and Hann, J., 1904, 85, 1358).

Although indications have been previously recorded (cf. Borsche and Niemann, *Annalen*, 1933, 502, 265) of the occurrence of isomeric products in reactions of this type, the case now described appears to be the first in which they have actually been isolated.

EXPERIMENTAL.

γ -Benzoyl-*n*-butyric Acid.—Aluminium chloride (16 g.) was gradually added to a cooled solution of glutaric anhydride (7 g., b. p. 140°/15 mm.) (Thole and Thorpe, J., 1912, 99, 1922; Kon and Thorpe, J., 1919, 115, 686) in benzene and after 12 hours the mixture was heated on a

water-bath until hydrogen chloride was no longer evolved. Benzene was removed by distillation, the product treated with dilute hydrochloric acid and cooled, and the final traces of benzene distilled in steam. The *keto-acid* was extracted with 10% sodium carbonate solution, precipitated by acidification, and recrystallised from hexane, forming needles (8.5 g.), m. p. 132° (Found : C, 68.5; H, 6.4; equiv., 191. $C_{11}H_{12}O_3$ requires C, 68.8; H, 6.2%; equiv., 192). The *semicarbazone*, prepared in hot alcoholic solution, crystallised in long needles, m. p. 213° (decomp.) (Found : C, 57.7; H, 6.2. $C_{12}H_{15}O_3N_3$ requires C, 57.8; H, 6.0%).

Reduction.—A mixture of γ -benzoyl-*n*-butyric acid (8 g.), zinc amalgam (12 g.), and concentrated hydrochloric acid (50 c.c.) was heated under reflux for 15 hours. The reduced acid was extracted in ether, transferred to sodium carbonate solution, precipitated by acidification, and again extracted in ether; after being dried and recovered, it solidified and recrystallisation from hexane gave δ -phenyl-*n*-valeric acid in rhombic crystals, m. p. 59° (Found for the silver salt : Ag, 38.1. Calc. for $C_{11}H_{13}O_2Ag$: Ag, 37.9%) (Baeyer and Jackson, *Ber.*, 1880, 13, 122).

γ -Benzoyl- $\beta\beta$ -dimethyl-*n*-butyric acid, prepared from the anhydride of $\beta\beta$ -dimethylglutaric acid (7 g.), benzene (15 c.c.), and aluminium chloride (14 g.), formed a heavy oil. It was extracted with ether, dried, and distilled under reduced pressure, b. p. 115°/35 mm. (Found : C, 70.7; H, 7.4; equiv., 218. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%; equiv., 220). Yield, 10 g. The *semicarbazone* crystallised slowly from alcohol in plates, m. p. 178° (decomp.) (Found : C, 60.9; H, 6.9. $C_{11}H_{13}O_3N_3$ requires C, 60.7; H, 6.9%).

δ -Phenyl- $\beta\beta$ -dimethyl-*n*-valeric acid, obtained by the Clemmensen method, formed a heavy oil, b. p. 120—121°/15 mm. (Found : C, 75.4; H, 8.8. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%).

γ -Benzoyl- β -methyl- β -ethyl-*n*-butyric acid crystallised from petroleum in plates, m. p. 49° (Found : C, 71.6; H, 7.8; equiv., 235. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%; equiv., 235). The *semicarbazone* slowly separated from dilute alcohol in small needles, m. p. 164—165° (Found : C, 61.8; H, 7.2. $C_{15}H_{21}O_3N_3$ requires C, 61.9; H, 7.2%).

δ -Phenyl- β -methyl- β -ethyl-*n*-valeric acid distilled as a heavy oil at 138°/20 mm. (Found : C, 76.2; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.1%).

The Reaction with β -Phenylglutaric Anhydride.—The product obtained from aluminium chloride (25 g.), β -phenylglutaric anhydride (20 g.), and benzene (20 c.c.) was freed from gummy impurities by trituration with benzene and extracted with aqueous sodium carbonate, and the crude solid obtained on acidification (m. p. 140—157°) was crystallised from alcohol. A sparingly soluble *substance* first separated in granules, m. p. 255—258°, which rose to 262° on recrystallisation (Found : C, 77.8; H, 5.5%). The more soluble portion consisted of 1-keto-hydrindene-3-acetic acid, which crystallised in thick rhombic plates, m. p. 155° (Found : equiv., 192. Calc. : equiv., 191). The *semicarbazone* crystallised from alcohol in needles, m. p. 260° (decomp.) (Speight, Stevenson, and Thorpe recorded m. p. 249°).

Benzylideneacetophenone (30 g.) was gradually added with shaking to a cooled suspension of ethyl sodiomalonate (prepared from 24 g. of ethyl malonate, 45 c.c. of absolute alcohol, and 3.5 g. of sodium), and the mixture was kept overnight, heated on a water-bath under reflux for 6 hours, poured into water, and acidified. An alcoholic solution of the viscous product deposited a neutral *substance* (5 g.) in hair-like needles, m. p. 255° after recrystallisation from glacial acetic acid (Found : C, 83.3; H, 5.9%). The brown oil obtained by evaporation of alcohol from the mother-liquor was heated with concentrated hydrochloric acid (50 c.c.) for 5 hours; γ -benzoyl- β -phenyl-*n*-butyric acid separated on cooling. The combined yield of this with that extracted by ether was 20 g. On recrystallisation from benzene it formed needles, m. p. 160°, and gave a *semicarbazone*, m. p. 220° (decomp.) (Qudrat-i-Khuda, *J. Indian Chem. Soc.*, 1931, 8, 218).

1-Phenacylcyclopentane-1-acetic acid, obtained from cyclopentane-1:1-diacetic anhydride (9 g.) (Kon and Thorpe, *loc. cit.*), separated from hexane in plates (8 g.), m. p. 85° (Found : C, 73.4; H, 7.4. $C_{15}H_{18}O_3$ requires C, 73.2; H, 7.3%). The *semicarbazone* crystallised from dilute alcohol in needles, m. p. 196° (decomp.) (Found : C, 63.2; H, 7.0. $C_{16}H_{21}O_3N_3$ requires C, 63.3; H, 7.0%).

1- β -Phenylethylcyclopentane-1-acetic acid, obtained on reduction of the *keto-acid* by the Clemmensen method, was a thick heavy oil (Found : C, 77.7; H, 8.7. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%). It was accompanied by a neutral substance, which appears to be the *lactone* of 1- β -hydroxy- β -phenylethylcyclopentane-1-acetic acid; on recrystallisation from benzene, it formed thick plates, m. p. 216° (Found : C, 78.75; H, 7.6. $C_{15}H_{18}O_2$ requires C, 78.3; H, 7.9%).

1-Phenacyl-3-methylcyclopentane-1-acetic acid crystallised from petroleum in small plates, m. p. 65° (Found : C, 73.7; H, 7.8; equiv., 262. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%; equiv., 260). The *semicarbazone* separated from dilute alcohol in light fibrous needles, m. p. 187° (decomp.) (Found : C, 64.5; H, 7.3. $C_{17}H_{23}O_3N_3$ requires C, 64.4; H, 7.2%).

1-*Phenacylcyclohexane-1-acetic acid* separated from hexane in needles, m. p. 99° (Found : C, 73·6; H, 7·6; equiv., 262. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%; equiv., 260). The *semi-carbazone* slowly crystallised from alcohol in plates, m. p. 189° (decomp.) (Found : C, 63·7; H, 7·5. $C_{17}H_{23}O_3N_3$ requires C, 64·4; H, 7·2%).

1- β -*Phenylethylcyclohexane-1-acetic acid*, obtained by the Clemmensen reduction of the keto-acid, was a heavy oil (Found : C, 77·8; H, 9·0. $C_{16}H_{22}O_2$ requires C, 78·0; H, 8·9%). The neutral product which accompanied this and appears to be the *lactone* of 1- β -hydroxy- β -phenylethylcyclohexane-1-acetic acid, crystallised from benzene in thick plates, m. p. 265° (Found : C, 78·9; H, 7·8. $C_{16}H_{20}O_2$ requires C, 79·3; H, 8·2%).

The Condensation of Phenylsuccinic Anhydride with Benzene.—The product obtained from phenylsuccinic anhydride (20 g.), dry benzene (15 c.c.), and anhydrous aluminium chloride (30 g.), was extracted with aqueous sodium carbonate. The neutral residue (2—2·5 g.), whose composition suggests that it is the lactone of a hydroxytriphenylbutyric acid, had m. p. 285° (decomp.) (Found : C, 83·8; H, 5·8. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·7%). The bulk of the crude acid (m. p. 102—110°), obtained from the aqueous sodium carbonate extract, dissolved in benzene, leaving a residue (3 g.) of β -benzoyl- β -phenylpropionic acid, which on recrystallisation from dilute alcohol formed cubic crystals, m. p. 168° (Found : C, 75·7; H, 5·5; equiv., 254. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·5%; equiv., 254). The $\beta\gamma$ -diphenylbutyric acid obtained on reduction by the Clemmensen method crystallised from alcohol in prisms, m. p. 95—96° (Ruhemann, J., 1910, 97, 459; Spring, J., 1934, 1332).

Fractional crystallisation of the benzene extract gave two fractions, m. p. 145—152° and 135—140°, and the mother-liquor slowly deposited small plates, m. p. 134°, which on recrystallisation from dilute alcohol gave α -benzoyl- α -phenylpropionic acid in needles, m. p. 154° (Found : C, 75·3; H, 5·6%; equiv., 256). On reduction this gave $\alpha\gamma$ -diphenyl-*n*-butyric acid, which crystallised from hexane in plates, m. p. 110° (Found : C, 79·8; H, 6·6. $C_{18}H_{16}O_2$ requires C, 80·0; H, 6·7%). The first two fractions consisted mainly of β -benzoyl- β -phenylpropionic acid, which was separated by extraction with benzene. The benzene extract furnished a further quantity of β -benzoyl- α -phenylpropionic acid. The isomeric acids were isolated in approximately equal proportion.

Synthesis of β -Benzoyl- β -phenylpropionic Acid and of β -Benzoyl- α -phenylpropionic Acid.—(A) Deoxybenzoin (5 g.) was gradually added to a solution of sodium ethoxide (prepared from 0·5 g. of sodium and 15 c.c. of absolute alcohol), and the mixture was treated with ethyl bromoacetate (4·2 g.) and heated on a water-bath under reflux for 5 hours. The viscous oil obtained by removal of alcohol and treatment with water was hydrolysed with alcoholic sodium hydroxide, and the acid was liberated by hydrochloric acid. On recrystallisation from dilute alcohol it formed thick cubes, m. p. 168° alone and when mixed with β -benzoyl- β -phenylpropionic acid obtained in the Friedel-Crafts reaction.

(B) 6 G. of phenylacetonitrile (b. p. 135—140°/35 mm.) were added to sodium ethoxide (1·2 g. of sodium, 15 c.c. of absolute alcohol), and the mixture gradually treated with ω -bromoacetophenone (10 g.). A solution of the product in alcohol was treated with potassium hydroxide (10 g., dissolved in the minimum quantity of water), and the mixture heated on the water-bath under reflux for 10 hours; ammonia was then no longer evolved. The acid obtained by purification through extraction with aqueous sodium carbonate and recrystallisation from alcohol had m. p. 154°, alone and when mixed with the specimen of β -benzoyl- α -phenylpropionic acid already described.

The condensation of glutaric anhydrides with other aromatic and hydroaromatic hydrocarbons is being investigated.