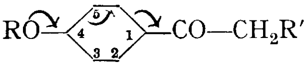
263. *The Hydrolytic Fission of Aromatic Ketones by Acids.*

By Peter Hill and W. F. Short.

It has long been known that acyl groups can frequently be removed from an aromatic nucleus by energetic treatment with phosphoric acid (Louise, *Ann. Chim.*, 1885, **6**, 206; Klages, *Ber.*, 1897, **30**, 1298; 1899, **32**, 1549; 1904, **37**, 1717; v. Auwers, *Annalen*, 1926, **447**, 176; *Ber.*, 1928, **61**, 1502), hydriodic acid (Meyer, *Ber.*, 1895, **28**, 1269, 3215; Klages, *Ber.*, 1899, **32**, 1556; 1904, **37**, 1715), hydrochloric acid (Meyer, *loc. cit.*; Weiler, *Ber.*, 1899, **32**, 1908), or sulphuric acid (Claus, *Ber.*, 1886, **19**, 2880; Elbs, *J. pr. Chem.*, 1887, **35**, 465; Hoogewerff and van Dorp, *Rec. trav. chim.*, 1902, **21**, 359; Morgan and Coulson, J., 1929, 2209), cleavage being facilitated by *o*-substituents. Removal of the side chain under milder conditions, such as those used in Stoermer's method for the demethylation of phenolic ethers (*Ber.*, 1908, **41**, 323), has seldom been encountered (Koenigs, *J. pr. Chem.*, 1900, **61**, 26; v. Auwers and Mauss, *Annalen*, 1928, **460**, 250). It has now been found that a number of aromatic ketones are decomposed by boiling with equal volumes of hydrobromic acid (*d* 1·5) and acetic acid. Comparative experiments showed that there is a continuous decrease in ease of fission in the series of deoxybenzoins *: (i) 4-*methoxy*-2 : 4′-*dimethyl* and 4-*methoxy*-2 : 2′-*dimethyl*, (ii) 4-*methoxy*-2-*methyl*, (iii) 4-methoxy-2-methylacetophenone (not a deoxybenzoin), (iv) 4′-*nitro*-4-*methoxy*-2-*methyl*, (v) 4-methoxy-, (vi) unsubstituted and 2′-*methyl*, the last two ketones being completely stable and (iv) and (v) undergoing slight decomposition. From these data it appears that fission (1) occurs only when the phenyl nucleus possesses a hydroxyl (methoxyl) group, (2) is facilitated by an *o*-methyl group in the same nucleus, (3) is retarded by a nitro-group in the benzyl nucleus. An *o*- or *p*-methyl group in the benzyl nucleus accelerates decomposition, and benzyl ketones are decomposed more readily than the corresponding methyl ketones.

Whatever the *detailed* mechanism of the reaction (the production of enolic and semiquinonoid forms is not excluded), it is evident that at some stage C_1 must accept a proton, and the influence of hydroxyl (methoxyl) is doubtless due to the electromeric change shown in (I). The effect of nitro- and methyl groups in the benzyl nucleus [I; $R' = C_6H_4{\cdot}NO_2(p)$ and $C_6H_4Me(p)$] is clearly due to decrease and increase respectively of the electron density at C_1 resulting from the general or inductive effects of these substituents (possibly relayed from the *p*-position; cf. Robinson, J., 1933, 1115). Retardation of fission by replacement of benzyl by methyl (I; $R' = H$) indicates that the benzyl group here exerts the same activating influence as in the nitration of guaiacol benzyl ether (Allan, Oxford, Robinson, and Smith, J., 1926, 407). The effect of hydroxyl may be correlated with its influence in the decarboxylation of benzoic acids (Cazeneuve, *Bull. Soc. chim.*, 1896, **15**, 73; Hoogewerff and van Dorp, *loc. cit.*; Hemmelmayr, *Monatsh.*, 1913, **34**, 365). *o*-Methyl and *p*-methoxyl in the phenyl nucleus also facilitate the reversal of the Fries transformation (Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56), and there are indications that in the case of methyl a polar factor is involved in addition to a steric effect.



(I.)

It has been stated that introduction of a chloromethyl group into toluene by means of *s*.-dichlorodimethyl ether (J., 1920, **117**, 520) or of paraform and hydrogen chloride (*Bull. Soc. chim.*, 1923, **33**, 313) affords *p*-xylyl chloride as sole product. It has now been shown by thermal analysis of the derived xylyl alcohols that a considerable amount of *o*-xylyl chloride (53 and 42% respectively in the two methods) is produced in addition to the *p*-isomeride (cf. I. G. Farbenind., D.R.-P. 500,912).

4-Methoxy-2-methyldeoxybenzoin affords 4-methoxy-2-methyldibenzyl on reduction by Clemmensen's method, but the product could not be converted into 4-hydroxy-1-methylphenanthrene by boiling with aluminium chloride in carbon disulphide solution (cf. Ruzicka and Hösli, *Helv. Chim. Acta*, 1934, **17**, 470).

EXPERIMENTAL.

Hydrolysis of Ketones.—The ketone (1 g.) was boiled gently (oil-bath) for 2 hrs. with hydrobromic acid (6 c.c.; *d* 1·5) and acetic acid (6 c.c.), the mixture concentrated in a vacuum, and the acid isolated by means of sodium carbonate. The phenols and hydroxy-ketones were isolated by means of sodium hydroxide and separated by distillation in steam. In cases where the ketones were not completely soluble in 12 c.c. of the mixed acids and it was desired to compare rates of decomposition, the experiments were repeated in homogeneous solution under identical conditions. The extent of fission was determined by weighing the acid produced and applying a solubility correction. When this method was not feasible (4′-nitro-4-methoxy-2-methyldeoxybenzoin and 4-methoxy-2-methylacetophenone) the phenolic fragment was isolated by exhaustive extraction with ether and estimated.

Preparation of Ketones.—2′-*Methyldeoxybenzoin.* *o*-Toluamide (20 g.) was added to an ethereal solution of benzylmagnesium chloride (from magnesium, 14·2 g.; benzyl chloride, 75 g.; in ether, 200 c.c.) at 0°, and the mixture boiled for 48 hrs. Decomposition with dilute acid furnished recovered amide (1·7 g.), some dibenzyl, and the *ketone* (9 g.; 32%), b. p. 172—

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* Substituents in the benzyl nucleus are indicated by 1′, 2′, etc.

173°/10 mm. It separates from methyl alcohol in colourless plates, m. p. *ca.* 18° (Found : C, 86·0; H, 6·95. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallises from ethyl acetate–alcohol in yellow plates, m. p. 146—147° (Found : N, 14·35. $C_{21}H_{18}O_4N_4$ requires N, 14·35%). The ketone (b. p. 318—320°) was prepared from *o*-toluic acid and phenylacetic acid by Mailhe (*Bull. Soc. chim.*, 1914, **15**, 325), but not characterised.

4-Hydroxydeoxybenzoin, obtained in 20% yield by Weisl's method (*Monatsh.*, 1905, **26**, 986), separates from alcohol in colourless prisms, m. p. 146—147° (Weisl, m. p. 142°, corr.), and does not suffer fission on boiling with hydrobromic–acetic acid.

4-*Methoxydeoxybenzoin.* The following method of preparation is superior to that of Ney (*Ber.*, 1888, **21**, 2450). Stannic chloride (1 mol.) was slowly added to anisole (1·1 mols.), phenylacetyl chloride (1 mol.), and benzene (10 mols.), and the temperature raised from 55° to 75° during 1 hr. The product after acidification afforded an 80% yield of crude ketone, b. p. 210—220°/10 mm. Recrystallisation from alcohol furnished the pure ketone, m. p. 77°. In this condensation and those subsequently described, a portion of the crude ketone does not solidify and probably contains some *o*-isomeride. The ketone was smoothly demethylated to the phenol, m. p. 146—147°, by boiling with hydrobromic-acetic acid.

4-*Methoxy*-2-*methyldeoxybenzoin* was obtained in poor yield from *m*-tolyl methyl ether, phenylacetyl chloride, and aluminium chloride in nitrobenzene solution, and was best prepared by boiling a mixture of phenylacetyl chloride (1 mol.), *m*-tolyl methyl ether (1·1 mols.), stannic chloride (1 mol.), and benzene (10 mols.) for 4½ hrs. The crude ketone, b. p. 213—214°/10 mm. (yield 60—70%), was purified by recrystallisation from methyl alcohol or light petroleum (b. p. 40—60°), from which it separated in long needles, m. p. 76·5° (Found : C, 80·0; H, 6·6. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%). The *semicarbazone* melts at 165—165·5° (Found : C, 68·5; H, 6·2; N, 13·8. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%). The ketone was completely converted into *m*-cresol (benzoate, m. p. 54°) and phenylacetic acid (m. p. and mixed m. p. 77°. Found : C, 70·8; H, 6·1. Calc. : C, 70·6; H, 5·9%) by boiling with hydrobromic–acetic acid under the standard conditions. When the ketone (1 g.) was boiled for 1½ hrs. with 70% potash (10 g.), 5-methoxy-*o*-toluic acid, m. p. and mixed m. p. 175—175·5°, was produced.

4-*Hydroxy*-2-*methyldibenzyl.* The above ketone (13 g.) was reduced by boiling for 6 hrs. with amalgamated zinc (30 g.) and dilute hydrochloric acid (1 : 1; 100 c.c.), 10 c.c. of concentrated hydrochloric acid being added every hour. 4-Methoxy-2-methyldibenzyl was obtained as a colourless oil, b. p. 180—190°/10 mm., which was recovered unchanged after boiling with aluminium chloride in carbon disulphide solution or with hydrobromic–acetic acid. Demethylation occurred when the ether (2·6 g.) was boiled for 2½ hrs. with acetic acid (27 c.c.) and hydriodic acid (60 c.c.; *d* 1·94) and the 4-hydroxy-2-methyldibenzyl so obtained was converted into the *benzoate*, which separated from 80% alcohol in radiating needles, m. p. 72—74° (Found : C, 83·3; H, 6·3. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%).

o-*Tolylacetic acid.* *o*-Xylyl alcohol was obtained in 39% yield by boiling paraform (30 g.) with benzylmagnesium chloride (from magnesium, 24 g.; benzyl chloride, 126 g.; in ether, 500 c.c.) for 54 hrs. The alcohol, b. p. 117—119°/20 mm., after repeated crystallisation from light petroleum (b. p. 40—60°), melted at 35·5—36° (cf. Grignard, *Bull. Soc. chim.*, 1903, **29**, 953; Tiffeneau and Delange, *Compt. rend.*, 1903, **137**, 573). *o*-Xylyl chloride, obtained in 88% yield from the alcohol (13 g.), pyridine (13 c.c.), and thionyl chloride (9·5 c.c.), distils at 92—94°/20 mm. The cyanide, b. p. 115—120°/10 mm., was obtained in 74% yield by adding the chloride (13 g.) in alcohol (14 c.c.) to sodium cyanide (7 g.) in water (7 c.c.) during ¼ hr. and boiling for 5 hrs. Hydrolysis of the cyanide (18 g.) by warming with equal volumes (18 c.c.) of sulphuric acid, acetic acid, and water, and finally boiling for 1 hr., afforded *o*-tolylacetic acid, m. p. 89·5—90° (yield 73%), which was converted into the chloride, b. p. 106—107°/10 mm., by heating to 90—100° for 2 hrs. with excess of thionyl chloride (yield 85%).

4-*Methoxy*-2 : 2′-*dimethyldeoxybenzoin.* Condensation of *o*-tolylacetyl chloride (45 g.) in benzene (200 c.c.) with *m*-tolyl methyl ether (33 g.) in presence of stannic chloride (30 c.c.) afforded a mixture (60% yield) of ketones, b. p. 220—225°/10 mm., which solidified on cooling. Recrystallisation from methyl alcohol gave colourless octahedral prisms, m. p. 97—98° (Found : C, 80·2; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate–methyl alcohol in orange plates, m. p. 188—189° (Found : N, 13·2. $C_{23}H_{22}O_5N_4$ requires N, 12·9%). Boiling with hydrobromic–acetic acid under the standard conditions caused complete fission of the ketone with formation of *o*-tolylacetic acid, m. p. and mixed m. p. 89·5—90°. 5-Methoxy-*o*-toluic acid, m. p. 174—176°, was produced when the ketone was boiled with 70% potash.

4-*Methoxy*-2 : 4′-*dimethyldeoxybenzoin* was prepared from *p*-xylyl alcohol in exactly the same way as the *o*-isomeride (above), the yields being approximately the same in each series. The ketone separated from methyl alcohol or light petroleum (b. p. 40—60°) in small prisms, m. p. 65—66° (Found : C, 80·4 ; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·2 ; H, 7·1%). The 2 : 4-*dinitrophenylhydrazone* forms brilliant scarlet plates (from ethyl acetate–methyl alcohol), m. p. 154·5—155·5° (Found : N, 13·0. $C_{23}H_{22}O_5N_4$ requires N, 12·9%). The ketone afforded 5-methoxy-*o*-toluic acid on digestion with 70% potash, and *p*-tolylacetic acid (m. p. and mixed m. p. 91—92°) on boiling with hydrobromic–acetic acid. A comparison between this ketone and 4-methoxy-2-methyldeoxybenzoin showed that in homogeneous solution under identical conditions fission occurs to the extent of 99% and 67% respectively.

4′-*Nitro-4-methoxy-2-methyldeoxybenzoin.* 4-Nitrophenylacetic acid ("Organic Syntheses," Coll. Vol. I, p. 398) was converted into the chloride (m. p. 47° ; yield 95%) by heating at 50—60° for 6 hrs. with thionyl chloride (2 mols.). The acid chloride (20·8 g.) was added in portions to an ice-cold solution of aluminium chloride (26·7 g.) in nitrobenzene (100 c.c.) and *m*-tolyl methyl ether (12·2 g.), the mixture then being allowed to warm to room temperature and finally maintained at 70—75° for 3½ hrs. The product, after decomposition with ice and hydrochloric acid and steam-distillation, was dissolved in hot methyl alcohol (charcoal) and allowed to crystallise. 4′-Nitro-4-methoxy-2-methyldeoxybenzoin separated, leaving the phenol (below) and resinous impurities in solution. The crude *methyl ether* (yield 63%) was recrystallised from boiling ligroin, and separated in long white plates, m. p. 92—93° (Found : C, 67·2 ; H, 5·2 ; N, 5·0. $C_{16}H_{15}O_4N$ requires C, 67·4 ; H, 5·3 ; N, 4·9%). It dissolves in dilute sodium hydroxide to a magenta solution, and affords an *oxime*, long needles, m. p. 164·5—165° (Found : N, 9·4. $C_{16}H_{16}O_4N_2$ requires N, 9·3%), from light petroleum–chloroform. Digestion of the ketone (1 g.) with 20% nitric acid (20 c.c.) for 4 hrs. furnished a mixture of acids, separated by chloroform into *p*-nitrobenzoic acid, m. p. 238°, and 5-methoxy-*o*-toluic acid, m.p. and mixed m. p. 174·5—175·5°. Only traces of *m*-cresol are produced when the ketone is boiled with hydrobromic and acetic acids under the standard conditions, the main product being the corresponding phenol.

4′-*Nitro-4-hydroxy-2-methyldeoxybenzoin.* The methyl-alcoholic mother-liquor (above) was evaporated to dryness, and extraction of the residue with boiling ligroin afforded long, white, silky needles (2 g.) of 4′-*nitro-4-hydroxy-2-methyldeoxybenzoin*, m. p. 128° (Found : C, 66·4 ; H, 4·7. $C_{15}H_{13}O_4N$ requires C, 66·4 ; H, 4·8%).

4-Methoxy-2-methylacetophenone (Barbier, *Helv. Chim. Acta*, 1928, **11**, 155) was decomposed by hydrobromic–acetic acid to the extent of 79% under conditions which led to complete fission of 4-methoxy-2-methyldeoxybenzoin.

o- *and* p-*Xylyl Chlorides.*—Condensation of toluene with paraform in presence of zinc chloride (Blanc, *Bull. Soc. chim.*, 1923, **33**, 313) or with *s*.-dichlorodimethyl ether and zinc chloride (Stephen, Short, and Gladding, J., 1920, **117**, 520) afforded a mixture of xylyl chlorides, b. p. 92—94°/20 mm., which was converted through the acetates (b. p. 118—119°/20 mm. : yield 70%) into a mixture of xylyl alcohols (b. p. 117—118°/20 mm. ; yield 87%). This mixture on freezing deposited *p*-xylyl alcohol, which after recrystallisation from chloroform–light petroleum (b. p. 40—60°) melted at 60—60·5°.

Freezing Points of Mixtures of o- *and* p-*Xylyl Alcohols.*—Although these substances have a rapid rate of crystallisation, their mixtures crystallise slowly, especially near the eutectic. The alcohols employed melted at 35·5—36° and 60—60·5° respectively in capillary tubes; their f. p.'s are somewhat lower. The following mean values for the f. p.'s were selected, the first number of each pair indicating the percentage of *o*-isomeride in the mixture : 100·0, 35·4° ; 92·1, 30·6° ; 86·2, 26·7° ; 76·1, 19·0° ; 66·4, 13·4° ; 43·6, 29·4° ; 33·3, 36·3° ; 25·2, 41·8° ; 18·0, 47·6° ; 12·4, 52·4° ; 4·1, 56·1° ; 0·0, 59·6°. The mixture prepared from Blanc's chloride had f. p. 30·5°, and therefore contained 41·7% of the *o*-alcohol. As a confirmation, a mixture of this alcohol (0·7373 g.) with *p*-xylyl alcohol (0·7096 g.) was found to freeze at 44·5°. Similarly, the mixed alcohols prepared from Stephen, Short, and Gladding's chloride froze at 22·4° and therefore contained 53·2% of the *o*-isomeride.

The isomeric pairs of chlorides, alcohols, acetates, and cyanides boil at the same temperature and cannot be separated by fractionation, whilst *o*- and *p*-tolylacetic acids form a continuous series of solid solutions.

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