59. *The Isomerisation of some Aromatic Ketones with Aluminium Chloride.*

By G. Baddeley.

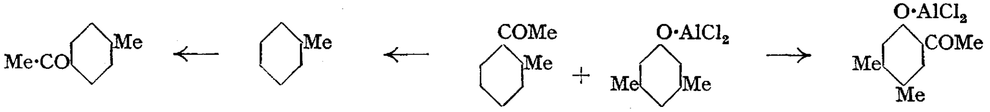
These isomerisations are shown to be of two types; the mechanism of each has been determined, and the factors controlling the relative amounts of isomerisation of each type are indicated. The migrations of alkyl groups in benzene homologues, phenols, aryl ketones, and hydroxyaryl ketones are related to one another and to the Jacobsen reaction.

It was suggested (J., 1943, 273) that elucidation of the isomerisation of 2-hydroxyaryl alkyl ketones by aluminium chloride required a study of the action of this reagent on alkylphenols and on aryl alkyl ketones. The former has already been contributed (J., 1943, 527) and the latter is now supplied.

The following isomerisations have been realised by the action of aluminium chloride :

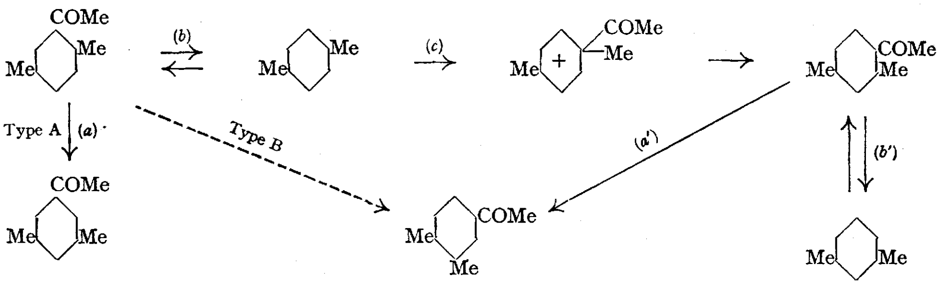
	Products of isomerisation.	
Initial ketone.	Type A.	**Type B.**
2-C_6H_4Me·COMe	None	4-C_6H_4Me·COMe (85%)
2-C_6H_4Me·COEt	None	4-C_6H_4Me·COEt (83%)
2 : 5-$C_6H_3Me_2$·COMe	3 : 5-$C_6H_3Me_2$·COMe (77%)	3 : 4-$C_6H_3Me_2$·COMe (8%)
2-C_6H_4Et·COMe	3-C_6H_4Et·COMe (70%)	4-C_6H_4Et·COMe (small)
2 : 5-$C_6H_3Et_2$·COMe	3 : 5-$C_6H_3Et_2$·COMe (83%)	None
2 : 4-$C_6H_3Me_2$·COMe	3 : 4-$C_6H_3Me_2$·COMe (80%)	None
2 : 4 : 6-$C_6H_2Me_3$·COMe	3 : 4 : 5-$C_6H_2Me_3$·COMe (87%)	None
2 : 5-$C_6H_3Me_2$·COPh	3 : 5-$C_6H_3Me_2$·COPh (90%)	None
5 : 8-Dimethyl-α-tetralone	5 : 7-Dimethyl-α-tetralone (90%)	None
4 : 7-Dimethyl-α-hydrindone	No change	

Acetophenone is converted into dypnone, $2\text{CPhMe:O} \longrightarrow \text{CPhMe:CH·COPh}$, when heated with less than 1 mol. of aluminium chloride (Calloway and Green, *J. Amer. Chem. Soc.*, **1937**, **59**, 809). This type of reaction can be suppressed by ensuring that the ketone is entirely engaged by the chloride, and unchanged acetophenone is recovered after treatment with excess of reagent at 150—180°. Under such conditions, at least 2 mols. of aluminium chloride being used, 2-methyl-aceto- and -propio-phenones are converted into the 4-methyl isomerides in excellent yield. If, however, the reaction be carried out in presence of *m*-5-xylenol, the yield of 4-methylacetophenone is halved owing to formation of 2-hydroxy-4 : 5-dimethylacetophenone, and it is thus reasonable to assume that the formation of an acylating agent is also responsible for the production of 4-methylacetophenone :



If an appreciable concentration of toluene were produced in the isomerisation of the *o*-tolyl ketone, the redistribution of alkyl groups, which this hydrocarbon is known to undergo in the presence of aluminium chloride, would be expected to lead to the presence of acetophenone and dimethylacetophenone among the products of the reaction. These, however, are not found.

Again, the subsidiary formation of 3 : 4-dimethylacetophenone from 2 : 5-dimethylacetophenone (the 3 : 5-isomeride being the main product) is completely suppressed by the presence of *m*-5-xylenol, and the reaction is perhaps best formulated as follows :



The acetylation of *p*-xylene to 2 : 4-dimethylacetophenone is assumed to involve a Wagner–Meerwein rearrangement and is related to the formation of *p*-*tert*.-butylacetophonone from *p*-di-*tert*.-butylbenzene by the action of acetyl chloride and aluminium chloride (Hennion and McLeese, *J. Amer. Chem. Soc.*, 1942, **64**, 2421). The Fries rearrangement of 4 : 6-dimethyl-2-ethylphenyl acetate to 2-hydroxy-3 : 5-dimethyl-4-ethylacetophenone (Auwers, *Annalen*, 1928, **460**, 240) is similarly explained. The conversion of 2 : 5- into 2 : 4-dimethylacetophenone is described later; it does not involve the isomerisation of *p*- to *m*-xylene, since this reaction is reversible and the conversion of 2 : 4- into 3 : 5-dimethylacetophenone has not been observed.

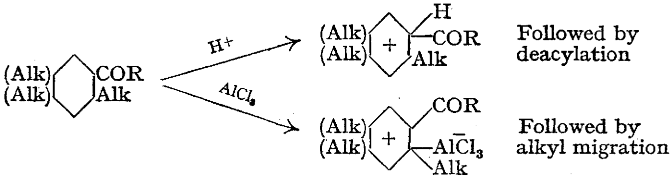
These isomerisations are of two types : (A) Those resembling the isomerisation of *o*-hydroxyaryl ketones, the mobile alkyl group moving intramolecularly into the neighbouring position, and (B) those involving the migration (possibly intramolecular) of the carbonyl group. The relative amounts of isomerisation of these two types are determined by the following factors which are indicated in the above diagram : (*a*) The mobility of the alkyl group, (*b*) the ease of fission of the acetyl group from the nucleus, (*c*) the probability of the resynthesis producing a different ketone.

Another alkyl group in the 4-position to the one undergoing migration was found to facilitate the type A isomerisation of *o*-hydroxyketones (J., 1943, 273); this effect, enhanced factor (*a*), explains the conversion of 2 : 5- into mainly 3 : 5-dimethylacetophenone, whereas 2-methyl- gives only 4-methyl-acetophenone. Again, the greater mobility of the ethyl group is now demonstrated by the conversion of 2- into 3-ethylacetophenone, and of 2 : 5- into 3 : 5-diethylacetophenone without the formation of the 3 : 4-isomeride.

Benzophenone is stable up to 200° with any amount of aluminium chloride, and the oxonium complex has been partly distilled under reduced pressure. In consequence of this stability, the isomerisation of 2 : 5- into 3 : 5-dimethylbenzophenone is shown to require more than 1 mol. of reagent. Again, the velocity constants for the isomerisation of 6-hydroxy-2 : 4- into 6-hydroxy-3 : 4-dimethylacetophenone in the presence of added 2 : 4- or 3 : 4-dimethylacetophenone show that both these ketones use only 1 mol. of reagent. Consequently, after oxonium complex formation, further additions of reagent act catalytically in isomerising aromatic ketones.

p-Hydroxyacetophenones undergo only isomerisations of type B, and the complete isomerisation of 4-hydroxy-2-methyl- into 2-hydroxy-4-methyl-acetophenone (Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56) was achieved with only a fraction over 1 mol. of aluminium chloride. Now the isomerisation of 2 : 5- into 2 : 4-dimethylacetophenone has been realised by heating the former with a mixture of 1 mol. of 6-hydroxy-3 : 4-dimethylacetophenone and 3 mols. (one being engaged by the ketone and two by the hydroxy-ketone) of aluminium chloride; this is an isomerisation of type B occurring under conditions where there is no reagent capable of producing an isomerisation of type A.

The acyl group which is displaced or the alkyl group which migrates is in the *o*-position to a bulky group, and it is suggested that it is this steric factor which determines the various changes now under discussion. Further, 5 : 8-dimethyl-α-tetralone undergoes isomerisation by aluminium chloride to its 5 : 7-isomeride and hydrolytic fission of the ketonic ring by phosphoric acid, whereas 4 : 7-dimethyl-α-hydrindone, with a *rigid* and *planar* structure, remains unchanged. This difference suggests that the isomerisation of an aromatic ketone requires the propulsion of the carbonyl group out of the plane of the aromatic nucleus. Since the migration of an alkyl group away from a carbonyl group requires the attachment of a second molecule of aluminium chloride, the first forming an oxonium complex, it was suggested (*Nature*, 1939, **144**, 444) that the orientation of the carbonyl group out of the plane of the nucleus inhibited, at least in part, the mesomeric effect of the carbonyl group and thus augmented the susceptibility of the nucleus to electrophilic attack. Moreover, since mobility is only conferred on the carbonyl group and an *o*-alkyl group, it was further suggested that the collisions between these two encourage a polarisation of the nucleus which enhances the electron availability at one or other of the positions to which these groups are attached (*loc. cit.*; *ibid.*, 1942, **150**, 178) :

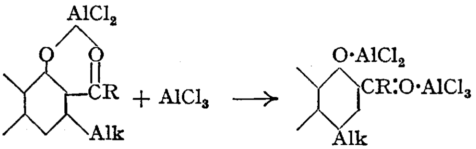


This readily explains why the isomerisation of type A is accelerated by an alkyl group in the *p*-position to the one undergoing migration.

The relative rates of deacylation and alkyl-group migration are revealed, since the former may not lead to an isomerisation of type B, by the addition of *m*-5-xylenol, which is acylated to a 2-hydroxy-4 : 5-dimethylaryl ketone. The results are summarised in the following table :

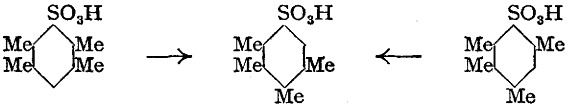
Initial ketone.	Recovered ketone.	Hydroxy-ketone.
2-C_6H_4Me·COMe	4-C_6H_4Me·COMe (42%)	40%
2 : 4-$C_6H_3Me_2$·COMe	3 : 4-$C_6H_3Me_2$·COMe (50%)	32%
2 : 5-$C_6H_3Me_2$·COMe	3 : 5-$C_6H_3Me_2$·COMe (75%)	8%
3 : 4-$C_6H_3Me_2$·COMe	3 : 4-$C_6H_3Me_2$·COMe (80%)	trace

All the isomerisations of *o*-hydroxyaryl ketones which have been examined are of type A. This does not signify that fission does not occur, but rather that it is completely reversible. This reversibility is due to the directing effect of the phenolic oxygen atom and the complete reversibility of the production of any *p*-hydroxyaryl ketone, coupled with (i) fission producing a symmetrical phenol homologue, or (ii) one *o*-position of the phenol nucleus being occupied by an alkyl group. Since both the hydroxyl and the carbonyl group usually use 1 mol. of aluminium chloride, a steric effect must account for the loss of only 1 mol. to a 6-hydroxy-2-alkylaryl ketone, and the isomerisation can, perhaps, be best formulated :



The isomerisation of aryl and hydroxyaryl ketones also occurs with aluminium bromide as reagent.

Homologues of benzonitrile are not isomerised by aluminium chloride; the nitrile group is linear and cannot collide with an *o*-alkyl group. Consequently, (i) the mesomeric effect of the nitrile group is not reduced by displacement of the nitrogen atom out of the plane of the nucleus, and (ii) the nitrile group as a whole and the neighbouring alkyl group as a whole are not displaced from the plane of the nucleus. On the other hand, homologues of benzenesulphonic acid can behave similarly to those of acetophenone : (i) an *o*-alkyl group facilitates the hydrolysis of the sulphonic acid, and (ii) an *o*-alkyl group can be displaced (by acid reagents); this is the Jacobsen reaction (*Ber.*, 1886, **19**, 1209), exemplified by :



Further, hexamethylbenzene was obtained from durene by the action of concentrated sulphuric acid; this disproportionation resembles those obtained by the action of aluminium chloride on benzene homologues.

The displacement by aluminium chloride of an alkyl group in an aromatic nucleus has been shown to require the juxtaposition of a bulky group. An acyl group (in an oxonium condition) provides this condition in the aromatic ketones and hydroxy-ketones, whereas the preliminary attachment of aluminium chloride is usually required with the homologues of benzene and phenol. The connection between a high electron availability of the nucleus and a ready intermolecular migration (J., 1943, 529) is now further illustrated by the aromatic ketones; no internuclear migration of alkyl groups occurs.

The rearrangement of the xylenes has been obtained (Norris and Vaala, *J. Amer. Chem. Soc.*, 1939, **61**, 2131) with only little disproportionation or decomposition; in consequence, the intramolecular migration of methyl groups by aluminium chloride has been obtained with aromatic hydrocarbons (at 50°), phenols (at 100—135°), and aromatic ketones and hydroxy-ketones (at 130—190°). The alkylation of phenols, acetophenone, and benzonitrile has been studied (later communications) and further illustrates that phenols and aromatic ketones have been isomerised without dealkylation and subsequent realkylation.

EXPERIMENTAL.

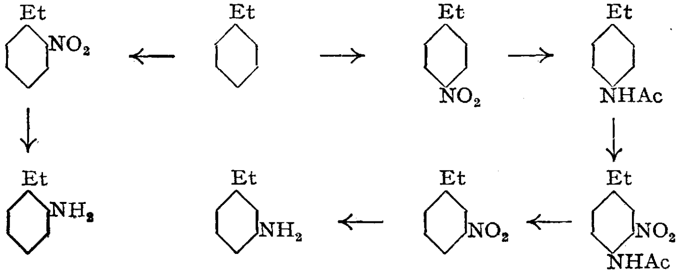
The ketones were mixed with aluminium chloride (2 mols.) and heated at 170° for 1·5 hours. The product was poured on ice, extracted with ether, dried over potassium carbonate, and distilled under reduced pressure. The products were identified by the m. p. and mixed m. p. of the semicarbazones.

2-Methylacetophenone (10 g.) and aluminium chloride (20 g.) produced 4-methylacetophenone (8·5 g.), and 2-methylpropiophenone (18 g.) and reagent (36 g.) produced 4-methylpropiophenone (15 g.). 2 : 5-Dimethylacetophenone (90 g.) and the chloride (170 g.) gave a product (75 g.), b. p. 118—122°/24 mm. After repeated fractional distillation, the first and the last fraction were identified as 3 : 5-dimethyl- and 3 : 4-dimethyl-acetophenone, respectively. The semicarbazone (m. p. 195—205°) of the mixture of ketones indicated 90% and 10% respectively of the two ketones.

2-Ethylacetophenone (9 g.) and reagent (18 g.) produced 3-ethylacetophenone (6·5 g.), contaminated with a little of the 4-isomeride. 2 : 5-Diethylacetophenone (53 g.) and aluminium chloride (84 g.) gave 3 : 5-diethylacetophenone (44 g.). Reduction by the Clemmensen method gave 1 : 3 : 5-triethylbenzene, identified by its trinitro- and tribromo-derivatives (m. p. 109° and 105—106°, respectively; Gattermann, Fritz, and Beck, *Ber.*, 1899, **32**, 1124). From alcohol, the former crystallised in long, colourless needles, m. p. 112° (Found: N, 14·1. Calc. for $C_{12}H_{15}O_6N_3$: N, 14·1%), and the latter had m. p. 105° (Found: Br, 60·0. Calc. for $C_{12}H_{15}Br_3$: Br, 60·2%). 2 : 4-Dimethylacetophenone (10 g.) and the chloride (20 g.) gave 3 : 4-dimethylacetophenone (8 g.). Mesityl methyl ketone (8 g.) and the chloride (16 g.) gave 3 : 4 : 5-trimethylacetophenone (7 g.), oxidised by alkaline hypochlorite to 3 : 4 : 5-trimethylbenzoic acid. 2 : 5-Dimethylbenzophenone (14 g.) and reagent (20 g.) were heated together at 190° for 2 hours. The recovered ketone (13 g.) crystallised from light petroleum (b. p. 40—60°) in stout, colourless needles, m. p. 70°, which did not depress the m. p. (70°) of 3 : 5-dimethylbenzophenone.

5 : 8-Dimethyl-α-tetralone (2 g.) and reagent (5 g.) gave 5 : 7-dimethyl-α-tetralone (1·8 g.), whereas 4 : 7-dimethyl-α-hydrindone and those ketones with no alkyl group in the *o*-position to the carbonyl group did not isomerise and were recovered to the extent of *ca.* 85%.

Preparation of the Ketones.—2- and 3-Methyl- and 2- and 3-ethyl-acetophenone and 2- and 3-methylpropiophenone were obtained in excellent yield from the appropriate homologue of benzonitrile (prepared from the corresponding amine) and the appropriate Grignard reagent. 2-Ethyl- and 3-ethyl-aniline were obtained in the following manner:



The mixture of mononitroethylbenzenes was separated by repeated fractional distillation. 3 : 5-Dimethylacetophenone was obtained in poor yield from acetonitrile and 3 : 5-dimethylphenylmagnesium bromide. 5-Bromo-*m*-xylene was obtained from *m*-4-xylidine.

5 : 8-*Dimethyl-α-tetralone.* β-(2 : 5-Dimethylbenzoyl)propionic acid (m. p. 62°, Muhr, *Ber.*, 1895, **28**, 3215) was obtained by shaking together molecular proportions of *p*-xylene, succinic anhydride, and aluminium chloride in carbon disulphide for 3 days. It crystallised from water in needles, m. p. 80° (Claus, *Ber.*, 1887, **20**, 1374, gives m. p. 84°). This ketone was reduced by Clemmensen's method to γ-(2 : 5-dimethylphenyl)butyric acid, b. p. 197°/30 mm., m. p. 70°. The acid chloride, obtained by addition of thionyl chloride, was dissolved in carbon disulphide, and aluminium chloride (1·2 mols.) added. Hydrogen chloride was readily evolved, and the tetralone was obtained as an oil, b. p. 164°/20 mm.

5 : 7-*Dimethyl-α-tetralone.* This was obtained from *m*-xylene in the manner described for the 5 : 8-isomeride. β-(2 : 4-Dimethylbenzoyl)propionic acid crystallised from dilute acetic acid in plates, m. p. 113° (Claus, *loc. cit.*, gives m. p. 108°), and γ-(2 : 4-dimethylphenyl)butyric acid in plates, m. p. 79° (Claus, *J. pr. Chem.*, 1892, **46**, 476, gives m. p. 70°).

4 : 7-*Dimethyl-α-hydrindone.* *p*-Xylene (10·6 g.), β-chloropropionic acid (10·9 g.), and aluminium chloride (15 g.) were heated together at 100° until evolution of hydrogen chloride ceased. Addition of water gave a solid aluminium salt, which was separated and decomposed with dilute sulphuric acid. β-(2 : 5-Dimethylphenyl)propionic acid was extracted with ether, dried over calcium chloride, and distilled; b. p. 183°/25 mm. (8 g.). The acid chloride was prepared by addition of thionyl chloride (6 g.), excess of which was removed at 100°/25 mm. Hydrogen chloride was readily evolved when aluminium chloride (7·5 g.) was added to a solution of the acid chloride in carbon disulphide (30 c.c.). The ketone was isolated in the usual manner; b. p. 150°/20 mm. (5 g.), and m. p. 77° after crystallisation from light petroleum (b. p. 60—80°) (Moureu, *Bull. Soc. chim.*, 1893, **9**, 572, gives m. p. 77—78°). All the other ketones were prepared by Friedel–Crafts reactions between the appropriate benzene homologue and acid chloride. 3 : 5-Dimethylbenzoyl chloride, required in the preparation of 3 : 5-*dimethylbenzophenone*, m. p. 70° (Found: C, 85·6; H, 6·9. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%), was obtained by oxidation of mesitylene by dilute nitric acid and subsequent addition of thionyl chloride to the resulting 3 : 5-dimethylbenzoic acid. *o*-Diethylbenzene, required in the preparation of 3 : 4-diethylacetophenone, was obtained by Clemmensen reduction of 2-ethylacetophenone.

Action of Aluminium Chloride in the Presence of m-5-*Xylenol.*—2 : 5-Dimethylacetophenone (10·8 g.), the xylenol (9·0 g.), and aluminium chloride (39 g.) were heated together at 160° for 4 hours. The mixture was then poured on ice, the ethereal extract washed with dilute sodium hydroxide solution, and dried over potassium carbonate. Pure 3 : 5-dimethylacetophenone (8·1 g.) was obtained on distillation. The alkaline washings were acidified with dilute sulphuric acid, and the ethereal extract dried over calcium chloride. The residue (*ca.* 1 g.), after removal of the xylenol by distillation, crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 74°, which did not depress the m. p. of 2-hydroxy-4 : 5-dimethylacetophenone. 2 : 4-Dimethylacetophenone (14 g.), the xylenol (12 g.), and aluminium chloride (42 g.) were treated as in the above experiment; 3 : 4-dimethylacetophenone (7 g.) and 2-hydroxy-4 : 5-dimethylacetophenone (6 g.) were obtained. 3 : 4-Dimethylacetophenone was treated exactly as in the previous experiment; unchanged ketone (11 g.) and traces of hydroxy-ketone were obtained. 2-Methylacetophenone (6 g.), the xylenol (7 g.), and aluminium chloride (40 g.) were treated as in the above experiments; 4-methylacetophenone (2·5 g.) and hydroxy-ketone (3·0 g.) were obtained.

Hydrolysis with Syrupy Phosphoric Acid.—All the *o*-alkylaryl ketones and 5 : 8-dimethyl-α-tetralone, but *not* 4 : 7-dimethyl-α-hydrindone, were readily hydrolysed by syrupy phosphoric acid at 180°, the carbonyl group becoming detached from the aromatic nucleus.

Isomerisations with Aluminium Bromide.—6-Hydroxy-2 : 4-dimethyl- and 2 : 4-dimethyl-acetophenone produced

2-hydroxy-4 : 5-dimethyl- and 3 : 4-dimethyl-acetophenone, respectively, when heated with aluminium bromide (3 mols.) at 150° for 3 hours. Quantitative measurements were not made, but the isomerisations appeared to occur at least as readily as when aluminium chloride was used.

Aluminium Chloride and Homologues of Benzonitrile.—2 : 5-Dimethylbenzonitrile (10 g.) and the reagent (22 g.) were heated together at 220—230° for an hour. Some darkening occurred, but unchanged nitrile (9 g.) was recovered. The corresponding acid amide was used for identification. Similarly, *o*-toluonitrile under the above conditions showed no isomerisation.

Isomerisation of 2 : 5-*Dimethyl- into* 2 : 4-*Dimethyl-acetophenone.*—2 : 5-Dimethylacetophenone (7·4 g.), *o*-4-xylenyl acetate (3·6 g.), and aluminium chloride (12·7 g.) were heated together at 160° for 5 hours. The recovered alkali-insoluble fraction (6 g.) was a mixture of 2 : 5-dimethyl- (*ca.* 70%) and 2 : 4-dimethyl-acetophenone. The semicarbazone of the former was less soluble in ethyl alcohol than was that of the latter.

2 : 4-*Dinitrophenylhydrazones.*

Ketone.	B. p.	M. p. of deriv.	N, %. Found.	N, %. Calc.
4-C_6H_4Et·COMe	114°	203°	17·1	17·1
2 : 5-$C_6H_3Et_2$·COMe	125	105	15·8	15·7
3 : 5- ,,	130	185	15·8	15·7
4-$C_6H_4Pr^{\alpha}$·COEt	131	147	15·9	15·7
2 : 5-$C_6H_3Pr^{\alpha}_2$·COMe	145	75	14·6	14·6

Semicarbazones.

Ketone.	B. p./20 mm.	M. p. of deriv.	N, %. Found.	N, %. Calc.
2-C_6H_4Me·COMe	94°	212°	22·2	22·0
3- ,,	102	205	22·1	,,
4- ,,	102	208	22·1	,,
2-C_6H_4Me·COEt	108	173	(a)	
3- ,,	115	178	(b)	
4- ,,	115	187	(c)	
2-C_6H_4Et·COMe	106	182	20·5	20·5
3- ,,	114	175	20·5	,,
4- ,,	114	191	20·6	,,
2 : 4-$C_6H_3Me_2$·COMe	110	202	20·4	20·5
2 : 5- ,,	110	168	(d)	
3 : 4- ,,	122	235	(e)	
3 : 5- ,,	118	219	20·6	,,
3 : 4-$C_6H_3Et_2$·COMe	133	180	17·9	18·0
3 : 5- ,,	130	149	18·2	,,
3 : 4 : 5-$C_6H_2Me_3$·COMe	138	217	19·3	19·2
α-Tetralone	127	226	20·7	20·7
5 : 7-Me_2-α-tetralone	170	245	18·1	18·2
5 : 8- ,,	164	222	18·2	,,
$C_6H_4Pr^{\alpha}$·COEt	131	143	18·0	18·0

(a) Blaise, *Compt. rend.*, 1901, **133**, 1218. (b) Wallach and Rentschler, *Annalen*, 1908, **360**, 62. (c) Auwers, *Annalen*, 1915, **408**, 243; *Ber.*, 1916, **49**, 2400. (d) Auwers, *loc. cit.* (e) Auwers and Kochritz, *Annalen*, 1907, **352**, 306.

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