527. *The Isomerisation of Aromatic Ketones.*

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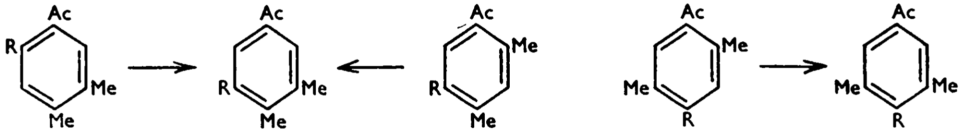
The isomerisation of 4-alkyl-2 : 5-dimethylacetophenone by fusion with excess of aluminium chloride affords the 3 : 5-dimethyl isomer in useful yield only when the 4-alkyl group is methyl, ethyl, or perhaps propyl. Other 4-alkyl groups are replaced by either a hydrogen atom or a methyl group.

The acetophenone homologues (I), (II), and (III), where R is an alkyl group, are readily accessible from *o*-, *m*-, and *p*-xylene respectively and, from previously published work,[1] might be expected to provide the otherwise not readily accessible ketones (IV) and (V) by rearrangement through the agency of hydrogen chloride–aluminium chloride. 1 : 3 : 5-Trialkylbenzenes are readily obtained by Friedel–Crafts alkylation and rearrangement of benzene homologues, and isomerisation of their acetyl derivatives may provide another route to the 3 : 4 : 5-trialkylacetophenones. It is already known [1] that 2 : 4 : 6-trimethylacetophenone gives the 3 : 4 : 5-isomer in 80% yield and that this isomer is the main product of attempts to isomerise 4-*tert*.-butyl-2 : 6-dimethylacetophenone; *i.e.*, that the *tert*.-butyl group is replaced by methyl group.[2] We have found other examples of this peculiar replacement. The isomerisation of 2 : 4 : 5-trialkylacetophenone is the more difficult step in the preparation of 3 : 4 : 5- from 2 : 4 : 6-trialkyl derivatives and thereby determines the feasibility of the preparation. This paper is concerned with the rearrangement of 2 : 4 : 5-trialkyl derivatives and especially that of 4-alkyl-2 : 5-dimethylacetophenone (III ⟶ V).



(I) (IV) (II) (III) (V)

The rearrangement is now shown to have very limited application : it provides compound (V) in better than 70% yield only when R is H, Me, or Et ; the yield is 39% when R is Pr, and the compound is not obtained when R is Pr^i, Bu^i, or CH$_2$Bu^t. Replacement of R by H accounts for 35 and 77% of the product when R is Pr and Pr^i, respectively, while replacement by Me provides 36 and 26% of the product when R is Bu^i and CH$_2$Bu^t, respectively.

The rearrangement (I ⟶ IV; R $\neq$ Me) requires a lower temperature and is more convenient than reaction (II ⟶ IV). Thus (IV; R = Pr) is obtained from (I) and (II; R = Pr) in yields of 49 and 31%, respectively. The propyl compound (II; R = Pr) also gave 2 : 4 : 5-trimethylacetophenone (10%).

Experimental

Materials.—4-Ethyl-2 : 5-dimethylacetophenone was prepared as described by Freund and Fleischer.[3]

2 : 5-*Dimethyl*-4-iso*propylacetophenone*.—The product of interaction of 2 : 5-dimethylacetophenone and methylmagnesium iodide gave 1 : 4-dimethyl-2-*iso*propenylbenzene, b. p. 190°/760 mm., by dehydration with formic acid (98%). Catalytic hydrogenation gave 1 : 4-*dimethyl*-2-iso*propylbenzene*, b. p. 190°/760 mm., n_D^{18} 1·5062 (Found : C, 89·4; H, 10·7. $C_{11}H_{16}$ requires C, 89·2; H, 10·8%). The required *ketone*, b. p. 151°/21 mm., n_D^{18} 1·5335, was obtained

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[1] Baddeley, *J.*, 1944, 232; 1950, 994; Baddeley and Pendleton, *J.*, 1952, 807; Baddeley, Holt, and Pickles, *J.*, 1952, 4162; Baddeley and Williamson, *J.*, 1953, 2120.

[2] Pearson and Bruton, *J. Org. Chem.*, 1954, **19**, 957.

[3] Freund and Fleischer, *Annalen*, 1918, **414**, 38.

by Friedel–Crafts acetylation in methylene chloride below 10°. Its *semicarbazone* separated from benzene in plates, m. p. 186° (Found: C, 67·7; H, 8·2; N, 17·2. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%), and its 2 : 4-*dinitrophenylhydrazone* from acetic acid in orange needles, m. p. 217° (Found: C, 61·6; H, 5·7; N, 15·6. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%). Oxidation of the ketone with dilute nitric acid gave benzene-1 : 2 : 4 : 5-tetracarboxylic acid (tetramethyl ester, m. p. and mixed m. p. 141°).

2 : 5-*Dimethyl*-4-n-*propylacetophenone*.—Clemmensen reduction of 2 : 5-dimethylpropiophenone[4] [*semicarbazone*, m. p. 169° (Found: C, 65·6; H, 7·6. $C_{12}H_{17}ON_3$ requires C, 65·8; H, 7·8%)] gave 1 : 4-dimethyl-2-*n*-propylbenzene,[5] n_D^{22} 1·5045, from which the required *ketone*, b. p. 146—147°/17 mm., n_D^{22} 1·5272, was obtained by acetylation. The *semicarbazone* separated from aqueous ethanol in rods, m. p. 160° (Found: C, 68·0; H, 8·7; N, 17·1. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%), and the 2 : 4-*dinitrophenylhydrazone* from acetic acid in orange flakes, m. p. 151·5° (Found: C, 61·8; H, 6·0; N, 15·4. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%). Tetramethyl benzene-1 : 2 : 4 : 5-tetracarboxylate was obtained from the ketone by oxidation and esterification.

4-*iso*Butyl-2 : 5-dimethylacetophenone was similarly prepared and identified. 2-iso*Butyl*-1 : 4-*dimethylbenzene*, b. p. 86°/14 mm., n_D^{19} 1·4981 (Found: C, 89·0; H, 10·7. $C_{12}H_{18}$ requires C, 88·9; H, 11·1%), gave the required ketone, b p. 150°/17 mm.; *semicarbazone*, m. p. 184° (Found: N, 16·2. $C_{15}H_{23}ON_3$ requires N, 16·1%), and 2 : 4-*dinitrophenylhydrazone*, m. p. 134—135° (Found: C, 62·7; H, 5·9; N, 15·2. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

2 : 5-*Dimethyl*-4-neo*pentylacetophenone*, b. p. 157°/17 mm., n_D^{22} 1·5230, was prepared from 1 : 4-dimethyl-2-*neo*pentylbenzene, b. p. 106°/22 mm., n_D^{23} 1·4985. The hydrocarbon was obtained in 50% yield by interaction under reflux for 3 hr. of the Grignard derivative of 2 : 5-dimethylbenzyl chloride[6] and a molecular proportion of *tert.*-butyl bromide; dry benzene was then added and the mixture was refluxed for a further 30 hr. The ketone gave a *semicarbazone*, m. p. 213° (Found: N, 15·4. $C_{16}H_{25}ON_3$ requires N, 15·3%), a 2 : 4-*dinitrophenylhydrazone*, m. p. 166° (Found: C, 62·8; H, 6·6; N, 13·9. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·5; N, 14·1%), and an *oxime*, needles, m. p. 134—135°, from aqueous methanol (Found: C, 76·7; H, 9·6; N, 5·9. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%).

4 : 5-Dimethyl-2-*n*-propylacetophenone, b. p. 150—151°/25 mm., $n_D^{21·5}$ 1·5245, was prepared from 1 : 2-dimethyl-4-*n*-propylbenzene,[7] and gave a *semicarbazone*, m. p. 131—132° (Found: C, 67·6; H, 8·6; N, 16·6. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 94° (Found: C, 61·7; H, 6·1; N, 15·0. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%).

2 : 4-Dimethyl-5-propylacetophenone, b. p. 142—144°/16 mm., n_D^{22} 1·5239 [*semicarbazone*, m. p. 144—145° (Found: C, 67·9; H, 8·6; N, 17·3. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%), and 2 : 4-*dinitrophenylhydrazone*, m. p. 173° (Found: C, 61·5; H, 5·8; N, 15·1. $C_{19}H_{22}O_4N_4$ requires C, 61·6; N, 5·9; N, 15·1%)], was prepared from 1 : 3-dimethyl-4-*n*-propylbenzene.[8]

The Isomerisation of the Ketones.—A mixture of the ketone, aluminium chloride (2·7 mol.) and sodium chloride (0·6 mol.) was heated for 4 hr. at a selected temperature and subsequently worked up in the usual manner.

2 : 4 : 5-Trimethylacetophenone [semicarbazone, m. p. 204° (Found: N, 19·3. Calc. for $C_{12}H_{17}ON_3$: N, 19·2%)] on reaction at 140° gave 3 : 4 : 5-trimethylacetophenone[1] (79%), b. p. 140—142°/18 mm. (semicarbazone, m. p. and mixed m. p. 217°).

4-Ethyl-2 : 5-dimethylacetophenone on reaction at 125° gave 4-ethyl-3 : 5-dimethylacetophenone (73%), b. p. 153—156°/22 mm., n_D^{18} 1·5410 [*semicarbazone*, m. p. 189—190° (Found: N, 18·3. $C_{13}H_{19}ON_3$ requires N, 18·0%)]. Oxidation of the product with dilute nitric acid gave benzene-1 : 2 : 3 : 5-tetracarboxylic acid (tetramethyl ester, m. p. and mixed m. p. 111°).

2 : 5-Dimethyl-4-propylacetophenone on reaction at 125° gave (*a*) 3 : 5-dimethylacetophenone (35%), which was identified by its semicarbazone and by oxidation to benzene-1 : 3 : 5-tricarboxylic acid, and (*b*) 3 : 5-dimethyl-4-propylacetophenone (39%), b. p. 107—109°/0·5 mm. [*semicarbazone*, m. p. 208—209° (Found: C, 68·0; H, 8·6; N, 17·3. $C_{14}H_{21}ON_3$ requires C,

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[4] Claus and Fickert, *Ber.*, 1886, **19**, 3183.
[5] Uhlhorn, *Ber.*, 1890, **23**, 2350.
[6] Braun and Nelles, *Ber.*, 1934, **67**, 1096.
[7] Auwers and Ziegler, *Annalen*, 1921, **425**, 260.
[8] Nightingale and Carton, *J. Amer. Chem. Soc.*, 1940, **62**, 280.

68·0; H, 8·5; N, 17·0%)]. It gave benzene-1 : 2 : 3 : 5-tetracarboxylic acid when oxidised with dilute nitric acid.

4-*iso*Butyl-2 : 5-dimethylacetophenone on reaction at 125° gave (*a*) 2 : 4 : 5-trimethylacetophenone (36%), which was identified by its semicarbazone, m. p. and mixed m. p. 204°, its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 246°, and by oxidation to benzene-1 : 2 : 4 : 5-tetracarboxylic acid; and (*b*) initial ketone (30%) which was similarly identified. It is remarkable that the 2-methyl group has not migrated to the 3-position.

2 : 5-Dimethyl-4-*neo*pentylacetophenone behaved similarly, affording 2 : 4 : 5-trimethylacetophenone (26%) and initial ketone (42%).

2 : 5-Dimethyl-4-*iso*propylacetophenone on reaction at 100° gave 2 : 5-dimethylacetophenone (77%), which was identified by its semicarbazone and by hypochlorite oxidation to 2 : 5-dimethylbenzoic acid, m. p. and mixed m. p. 132°.

4 : 5-Dimethyl-2-propylacetophenone on reaction at 100° gave 3 : 4-dimethylacetophenone (22%) and 3 : 4-dimethyl-5-propylacetophenone (49%), b. p. 155—158°/17 mm. [*semicarbazone*, m. p. 155—155·5° (Found : C, 68·3; H, 8·2; N, 17·1. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5; N, 17·0%), and 2 : 4-*dinitrophenylhydrazone*, m. p. 171—172° (Found : C, 61·8; H, 5·8; N, 15·2. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%)]; it gave benzene-1 : 2 : 3 : 5-tetracarboxylic acid when oxidised with dilute nitric acid.

2 : 4-Dimethyl-5-propylacetophenone on reaction at 125° gave 2 : 4 : 5-trimethylacetophenone (10%), initial ketone (10%), and 3 : 4-dimethyl-5-propylacetophenone (31%).

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