

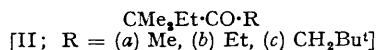
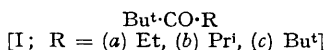
*The Synthesis and Reactions of Branched-chain Hydrocarbons. Part IX.**
The Preparation of some Branched-chain Alcohols and Ketones.

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The preparation of some branched-chain alcohols and ketones by the Grignard reaction from acid chlorides and acid anhydrides is described.

FOR other investigations it was necessary to prepare the substituted dialkyl ketones (I) and (II), and the corresponding alcohols, in quantity and in a high degree of purity.



2 : 2-Dimethylpentan-3-one (Ia) and 3 : 3-dimethylpentan-2-one (IIa) were prepared by the interaction of the appropriate Grignard reagent and acid anhydride at -70° (cf. Newman and Smith, *J. Org. Chem.*, 1948, **13**, 592). This appears to be a more convenient and satisfactory method than that described by Whitmore *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 683; 1942, **64**, 2964). In the preparation of 4 : 4-dimethylhexan-3-one (IIb) from *tert.*-pentylmagnesium chloride and propionic anhydride the yield of ketone was reduced by concurrent formation of *n*-propyl propionate. Use of this method to obtain the more highly substituted ketone, 2 : 2 : 4-trimethylpentan-3-one (Ib), was even less successful. A better approach to the remaining ketones (Ib, Ic, and IIc) was found in the reaction between the appropriate acid chloride and Grignard reagent in the presence of cuprous chloride or copper (Cook *et al.*, *ibid.*, 1949, **71**, 1509, 4141). Thus 2 : 2 : 5 : 5-tetramethylheptan-4-one (IIc) was prepared from *tert.*-pentylmagnesium chloride and 3 : 3-dimethylbutanoyl chloride; † 3 : 3-dimethylbutan-1-ol and its ester with 3 : 3-dimethylbutanoic acid were also formed. 2 : 2 : 4-Trimethylpentan-3-one (Ib) was similarly prepared from pivaloyl chloride and *isopropylmagnesium chloride*, and although the yield was only moderate the method was more convenient for the large-scale preparation of the pure ketone than the methylation of 2 : 4-dimethylpentan-3-one (Whitmore and Stahley, *ibid.*, 1933, **55**, 4155). Attempts to prepare 2 : 2 : 4-trimethylhexan-3-one (Ic) by addition of *sec.*-butylmagnesium chloride to pivaloyl chloride gave an inseparable

* Part VIII, *J.*, 1955, 1781.

† Geneva nomenclature, $\text{CO}_2\text{H} = 1$.

mixture of the required ketone, neopentyl alcohol, and neopentyl pivalate. Reversal of the order of mixing the reagents gave, even in the presence of cuprous chloride, mainly neopentyl alcohol. The ketone was eventually obtained by the oxidation of 2:2:4-trimethylhexan-3-ol, which was prepared in good yield by adding α -methylbutyryl chloride to an excess of *tert.*-butylmagnesium chloride.

EXPERIMENTAL

Reaction of Grignard Reagents with Acid Anhydrides.—A filtered solution of the Grignard reagent, prepared from the alkyl halide (5.0 mole), magnesium (121.6 g.), and ether (1200 c.c.) by Whitmore and Badertscher's method (*J. Amer. Chem. Soc.*, 1933, **55**, 1559), was added during 12 hr. to a stirred solution of the acid anhydride (5.0 mole) in ether (300 c.c.) and the mixture was kept at -70° . Stirring was continued for a further 2 hr., and the mixture allowed to warm to 0° and then decomposed by the dropwise addition of a solution of ammonium chloride (321 g.) in water (2 l.). The ethereal layer was separated, the aqueous layer was extracted with ether (3×200 c.c.), and the combined ethereal solutions were washed with 10% aqueous sodium hydroxide (2×600 c.c.) and water. The washings were extracted with ether (3×100 c.c.). After being dried (Na_2SO_4), the ether was removed from the combined ethereal solutions, and the residue fractionally distilled through a 50-cm. column packed with Dixon gauze. In this way were prepared: (a) From *tert.*-butyl chloride and propionic anhydride, 2:2-dimethylpentan-3-one (269 g.), b. p. $125-126^\circ$, n_D^{20} 1.4050 [2:4-dinitrophenylhydrazone, orange (from aqueous alcohol), m. p. $174-175^\circ$]; Whitmore, Noll, and Meunier (*ibid.*, 1939, **61**, 683) record b. p. $124.5^\circ/729$ mm., n_D^{20} 1.4049—1.4052. Kharasch, Sternfeld, and Mayo (*J. Org. Chem.*, 1940, **5**, 362) give 2:4-dinitrophenylhydrazone, m. p. 175° . (b) From *tert.*-pentyl chloride and acetic anhydride, 3:3-dimethylpentan-2-one (175 g.), b. p. $131-132^\circ$, n_D^{20} 1.4098—1.4100 [2:4-dinitrophenylhydrazone, yellow felted needles (from aqueous alcohol), m. p. 112°]; Whitmore and Lewis (*J. Amer. Chem. Soc.*, 1942, **64**, 2964) record b. p. $130^\circ/733$ mm., n_D^{20} 1.4100, and 2:4-dinitrophenylhydrazone, m. p. 112° . (c) From *tert.*-pentyl chloride and propionic anhydride, *n*-propyl propionate (37.8 g.), b. p. $122-124^\circ$, n_D^{20} 1.3936 [Tischtschenko (*Chem. Zentr.*, 1906, II, 1552) records b. p. $122-124^\circ$], and 4:4-dimethylhexan-3-one (105 g.), b. p. $150.5-151.5^\circ$, n_D^{20} 1.4163—1.4165 [2:4-dinitrophenylhydrazone, yellow needles (from aqueous alcohol), m. p. 86° (Found: C, 54.7; H, 6.6; N, 17.9. $\text{C}_{14}\text{H}_{20}\text{O}_4\text{N}_4$ requires C, 54.5; H, 6.5; N, 18.2%), semicarbazone, white plates (from light petroleum, b. p. $60-80^\circ$), m. p. $97-98^\circ$]. Parry (*J.*, 1915, 110) records b. p. $150-152^\circ$, and semicarbazone, m. p. $97-98^\circ$. (d) From isopropyl bromide and pivalic anhydride (see below) (on 0.2-mole scale), a fraction (2.4 g.), b. p. $60-130^\circ$, containing pivalaldehyde (2:4-dinitrophenylhydrazone, m. p. and mixed m. p. 208°) and 2:2:4-trimethylpentan-3-one (3.9 g.), b. p. 132° , characterised by reduction with lithium aluminium hydride to 2:2:4-trimethylpentan-3-ol (3:5-dinitrobenzoate m. p. and mixed m. p. $104-106^\circ$).

Pivalic Anhydride.—A mixture of pivalic acid (50 g.) and acetic anhydride (90 g.) was slowly distilled through a 12" helix-packed column at such a rate that the vapour temperature at the top of the column did not exceed 120° . When the temperature rose above 120° , acetic anhydride (10 c.c.) was added and the above procedure repeated. Fractional distillation of the residue through an efficient column gave pivalic anhydride (35.7 g.), b. p. $78^\circ/12$ mm., n_D^{20} 1.4089 [Butlerow (*Annalen*, 1874, **173**, 374) records b. p. 190°]. On treatment with aniline, only pivalanilide, m. p. and mixed m. p. 134° , was formed [Found: *M* (by hydrolysis), 181.2. Calc. for $\text{C}_{10}\text{H}_{18}\text{O}_3$: *M*, 186].

2:2:4-Trimethylpentan-3-one.—A filtered solution of the Grignard reagent prepared from isopropyl chloride (392 g., 5 mole) and magnesium (120 g., 5 g.-atom) in ether (1 l.) was added during 4 hr. to a well-cooled (ice-salt) stirred mixture of pivaloyl chloride (622 g., 5 mole) cuprous chloride (7 g.), copper powder (1 g.), and ether (1.5 l.). Stirring was continued overnight, while the mixture warmed to room temperature. It was then poured on crushed ice (1.5 kg.) and concentrated hydrochloric acid (550 c.c.), the ethereal layer separated, and the aqueous layer extracted with ether. The combined ethereal solutions were washed with 5% sodium hydroxide solution (4×250 c.c.), then dried (CaCl_2), and ether removed through a 60-cm. column packed with single turn Fenske helices. The products from two such preparations were combined and fractionally distilled through a 60-cm. column packed with Dixon gauzes to yield a mixture (9.3 g.), b. p. $>60^\circ/88$ mm., of pivalaldehyde (2:4-dinitrophenylhydrazone, m. p. and mixed m. p. $210-211^\circ$) and isopropyl alcohol (3:5-dinitrobenzoate, m. p. and mixed m. p. 122°);

2 : 2 : 4-trimethylpentan-3-one (456 g.), b. p. 61.5—63°/79 mm., n_D^{20} 1.4030—1.4054 (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166—167°); and a non-homogenous fraction (272 g.), b. p. 83—104°/77 mm., containing *neopentyl* pivalate (identified by hydrolysis to pivalic acid and *neopentyl* alcohol) and 2 : 4 : 4-trimethylpentan-3-ol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 105—106°).

2 : 2 : 5 : 5-Tetramethylheptan-4-one.—A filtered solution of the Grignard reagent prepared from *tert.*-pentyl chloride (106 g., 1 mole) and magnesium (24 g.) in ether (300 c.c.) was added during 2 hr. to a well-cooled (ice-salt) stirred (copper stirrer) mixture of cuprous chloride (1 g.) and 3 : 3-dimethylbutanoyl chloride (96 g.) in ether (500 c.c.). The subsequent procedure was as described above. Fractional distillation of the residue obtained after removal of the ether gave: (a) A mixture (4.3 g.) of unsaturated material and 3 : 3-dimethylbutan-1-ol, b. p. 30°/14 mm. (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 83.5°). (b) 2 : 2 : 5 : 5-Tetramethylheptan-4-one (46.3 g.), b. p. 60—70°/14 mm., n_D^{20} 1.4240—1.4242 (b. p. 70°/14 mm., n_D^{20} 1.4242 on analytical sample) (Found : C, 77.9; H, 12.9. $C_{11}H_{22}O$ requires C, 77.5; H, 13.0%). No carbonyl derivative could be obtained. Reduction of the ketone with lithium aluminium hydride gave 2 : 2 : 5 : 5-tetramethylheptan-4-ol, b. p. 83°/14 mm., n_D^{20} 1.4406 (Found : C, 76.7; H, 14.0. $C_{11}H_{24}O$ requires C, 76.6; H, 14.0%) {3 : 5-dinitrobenzoate [from light petroleum (b. p. 40—60°)], m. p. 108° (Found : C, 59.0; H, 7.1; N, 7.6. $C_{18}H_{26}O_6N_2$ requires C, 59.0; H, 7.1; N, 7.7%)} (cf. Ansell, Hickinbottom, and Hyatt, *J.*, 1955, 1592). (c) A fraction (16.1 g.), b. p. 70—75°/14 mm., which on redistillation gave the above ketone and 3 : 3-dimethylbutyl 3 : 3-dimethylbutanoate (8.3 g.), b. p. 94°/17 mm., m. p. and mixed m. p. 22° (cf. Whitmore Mattil and Popkin, *J. Amer. Chem. Soc.*, 1938, 60, 2790).

2 : 2 : 4-Trimethylhexan-3-one and 2 : 2 : 4-Trimethylhexan-3-ol.—(a) A filtered solution of the Grignard reagent prepared from *sec.*-butyl chloride (92 g., 1 mole) and magnesium (24.3 g., 1 g.-atom) in ether (220 c.c.) was added during 1½ hr. to a well-cooled (ice-salt) mixture of pivaloyl chloride (120 g., 1 mole), cuprous chloride (3 g.), and copper powder (10 g.) in ether (400 c.c.). The subsequent procedure was as in the previous examples. Fractional distillation of the residue obtained after removal of the ether gave: a fraction, b. p. <38°, containing pivalaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 210—211°); a fraction, b. p. 87—90°/80 mm., containing *neopentyl* alcohol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 90—91°), 2 : 2 : 4-trimethylhexan-3-one [2 : 4-dinitrophenylhydrazone, yellow needles (from aqueous alcohol), m. p. 130—130.5° (Found : C, 55.6; H, 7.0; N, 17.2. $C_{15}H_{22}O_4N_4$ requires C, 55.9; H, 6.9; N, 17.4%)], and *neopentyl* pivalate (identified by the formation of pivalic acid on hydrolysis).

(b) Pivaloyl chloride (120 g., 1 mole) was added during 5 hr. to a stirred, filtered solution of the Grignard reagent prepared from *sec.*-butyl chloride (276 g., 3 mole) and magnesium (72 g., 3 g.-atom) in ether (1.2 l.). It was then poured on a mixture of ice and sulphuric acid. The subsequent procedure was as in the previous examples. Fractional distillation of the residue obtained on removal of the ether from the dried ($MgSO_4$) ethereal extracts gave, after a small fore-run, *neopentyl* alcohol (56 g.), b. p. 114—116° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 91°).

(c) α -Methylbutyryl chloride (348 g., 2.9 mole) was added during 5 hr. to a stirred, filtered solution of the Grignard reagent prepared from *tert.*-butyl chloride (883 g., 9.6 mole) and magnesium (234 g., 9.6 g.-atom) in ether (3.7 l.). The subsequent procedure was as in (b). The distillate from three combined runs gave *tert.*-butyl alcohol (80 g.), b. p. 76—80° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 141—142°), 2-methylbutan-1-ol (20 g.), b. p. 126—128° (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 68—69°), and 2 : 2 : 4-trimethylhexan-3-ol (672 g.), b. p. 171—172° [phenylurethane, m. p. 78—80° [Haller and Bauer (*Compt. rend.*, 1910, 150, 582) record m. p. 78°]. Oxidation of the alcohol with chromium trioxide in acetic acid gave 2 : 2 : 4-trimethylhexan-3-one, isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 130°.

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