411. *The Preparation and Dehydration of 2-Methyl-6-phenylheptan-3-ol.*

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Dehydration of 2-methyl-6-phenylheptan-3-ol with different reagents gave 2-methyl-6-phenylhept-2-ene, with minor amounts of the hept-3-ene. Reaction of the alcohol with hydrobromic acid followed by dehydrobromination yielded the hept-2-ene.

As a preliminary step in an investigation into the regulated degradation of sterol side-chains the preparation of 2-methyl-6-phenylheptan-3-ol (I) was undertaken. This compound has the same side-chain as 24-hydroxycholesterol. The alcohol was prepared from styrene, which was converted into 1-bromoethylbenzene and thence into 1-phenylethylmalonic acid; decarboxylation of the latter gave β-phenylbutyric acid which was reduced to 3-phenylbutan-1-ol and then converted successively into 1-bromo-3-phenylbutane and, by a Grignard reaction with *iso*butaldehyde, into 2-methyl-6-phenylheptan-3-ol (I). The various stages in this synthesis were accomplished by standard reactions. All the compounds are liquids and no crystalline derivative of the desired alcohol, which has two asymmetric carbon atoms, was obtained. However, oxidation gave 2-methyl-6-phenylheptan-3-one, which was characterised as the crystalline 2 : 4-dinitrophenylhydrazone.

Simonsen and his co-workers (*J.*, 1939, 1504) showed that (—)-α-curcumene consists of a mixture of 2-methyl-6-*p*-tolylhept-1- and -2-ene. This mixture was prepared in an optically inactive form by Carter, Simonsen, and Williams (*J.*, 1940, 451) from 2-methyl-6-*p*-tolylheptan-2-ol, which was synthesised in a manner not unlike that used in the present work. This alcohol was dehydrated with potassium hydrogen sulphate to a mixture of the hept-1-ene and the hept-2-ene with the former predominating.

The dehydration of 2-methyl-6-phenylheptan-3-ol has now been studied using a number of reagents. Comparatively few extensive studies on the dehydration of secondary alcohols of the type $(CH_3)_2CH{\cdot}CH(OH){\cdot}CH_2R$ are found in the literature. Tuot (*Compt. rend.*, 1940, **211**, 561) dehydrated a number of secondary alcohols including 2-methylheptan-3-ol with anhydrous copper sulphate and concluded that where the hydroxyl group is adjacent to a tertiary carbon atom, dehydration takes place exclusively towards that atom. Henne and Matuszak (*J. Amer. Chem. Soc.*, 1944, **66**, 1649) dehydrated several alcohols by various methods and investigated the products by ozonolysis. One of the compounds they studied was 2-methylpentan-3-ol, from which three isomeric pentenes were obtained. The results show that none of the methods employed gives a single isomer, but that, in general, but not invariably, dehydration favours the formation of 2-methylpent-2-ene rather than 4-methylpent-2-ene. The chief course of the dehydration again involves the tertiary carbon atom.

In selecting methods for the dehydration of 2-methyl-6-phenylheptan-3-ol (I), it was borne in mind that the reagents used must be capable of being applied to 24-hydroxycholesterol. Of the two most likely products 2-methyl-6-phenylhept-2-ene (II) will give on ozonolysis acetone and 3-phenylvaleraldehyde, whereas 2-methyl-6-phenylhept-3-ene (III) will give *iso*butaldehyde and 2-phenylbutaldehyde. The 2 : 4-dinitrophenylhydrazones of these carbonyl compounds were readily separated by chromatography on alumina so that each could be estimated. In this way the approximate yields of the heptenes given in the Table were obtained.

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH(CH_3)_2$
(I)

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}C(CH_3)_2$
(II)

$Ph{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH(CH_3)_2$
(III)

$Ph{\cdot}C(CH_3){:}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3)_2$
(IV)

When potassium hydrogen sulphate was used for dehydration two treatments were necessary for complete reaction. The use of phosphoric oxide in benzene resulted in the formation of a complex mixture. On ozonolysis acetone and acetophenone were obtained, indicating the presence of 6-methyl-2-phenylhept-2-ene (IV) as well as 2-methyl-6-phenylhept-2-ene (II).

The product obtained by treating 2-methyl-6-phenylheptan-3-ol (I) with hydrobromic acid was shown by analysis to have lost hydrogen bromide during distillation. Completion of the dehydrobromination with collidine gave 2-methyl-6-phenylhept-2-ene (II), identified by conversion on ozonolysis into acetone and a phenylvaleraldehyde, isolated as 2 : 4-dinitrophenylhydrazones. No reference has been found in the literature to this aldehyde, but from analysis and the mode of formation it must be 3-phenylvaleraldehyde. It differs from 4-phenylvaleraldehyde prepared by Braun and Kruber (*Ber.*, 1912, **45**, 399).

Method	2-Methyl-6-phenylheptenes obtained
Anhyd. $KHSO_4$ at 160°	Hept-2-ene, 90% Hept-3-ene, 10%
$KHSO_4$ in boiling xylene	Hept-3-ene, 20% Hept-2-ene, 80%
P_2O_5 in boiling benzene	Hept-2-ene, 70% Hept-5-ene, 30%
$POCl_3$ in boiling pyridine	Hept-2-ene
Reaction with HBr, followed by dehydrobromination	Hept-2-ene

The results obtained during the present work substantiate the general conclusions of Tuot (*loc. cit.*) and of Henne and Matuszak (*loc. cit.*) that in secondary alcohols of this type dehydration chiefly involves the elimination of hydrogen from the tertiary carbon atom.

EXPERIMENTAL

Solutions in organic solvents which are described as having been washed and dried were washed with dilute sulphuric acid and/or aqueous sodium carbonate (5%), then with water, and dried (Na_2SO_4 or $CaCl_2$).

Ethyl 1-*Phenylethylmalonate*.—1-Bromoethylbenzene, b. p. 77°/5 mm., was prepared by Ashworth and Burkhardt's method (*J.*, 1928, 1796).

Anhydrous ethanol (250 ml.) was added to sodium (11·5 g., 1 mol.) and when the sodium had dissolved the solution was refluxed for 5 min. (moisture excluded throughout). After the addition of ethyl malonate (80 g., 1 mol.), 1-bromoethylbenzene (90 g., 1 mol.) was dropped in so that the solution boiled gently. After addition was complete, boiling under reflux was continued for 5 hr. When cold, sodium bromide was filtered off and excess of alcohol was evaporated. The solution was diluted with water and extracted with ether. The ethereal extracts were washed, dried, and concentrated. The residue was fractionated and yielded ethyl 1-phenylethylmalonate (100 g., 78%), b. p. 156—157°/7 mm. Fischer and Schmidt (*Ber.*, 1906, **39**, 351) record b. p. 185—187°/24 mm.

Ethyl β-*Phenylbutyrate.*—1-Phenylethylmalonic acid (40·6 g.), m. p. 141—143°, prepared by hydrolysis of the above ester with aqueous-alcoholic potassium hydroxide, was heated at 180—190° for 30 min. Distillation under reduced pressure yielded β-phenylbutyric acid (30 g., 93%), b. p. 168°/17 mm., m. p. 36—38·5°. Rupe (*Annalen*, 1909, **369**, 323) records m. p. 39—40°.

This acid (35 g.) with concentrated sulphuric acid (2 ml.) in ethanol (100 ml.) at the b. p. (2 hr.) gave the ethyl ester (35 g., 85%), b. p. 128—131°/15 mm. B. p. 111°/4 mm. has been recorded for this ester (Levene and Marker, *J. Biol. Chem.*, 1931, **46**, 1266)

3-*Phenylbutan*-1-*ol.*—(*a*) Ethyl β-phenylbutyrate (20 g.) in anhydrous ethanol (100 ml.) was added dropwise to a fine suspension of molten sodium in warm toluene at a rate sufficient to maintain boiling (moisture excluded). Boiling under reflux was continued for 2 hr. after addition was complete. Ethanol (100 ml.) was then added to dissolve excess of sodium, and the solution was poured into water (300 ml.). The usual methods gave recovered β-phenylbutyric acid (1 g.) and 3-phenylbutanol (9·5 g., 64%), b. p. 121—122°/10 mm. Braun, Grabowski, and Kirschbaum (*Ber.*, 1913, **46**, 1266) give b. p. 134°/16 mm.

(*b*) β-Phenylbutyric acid (82 g.) in ether (400 ml.) was added to lithium aluminium hydride (22 g.) in ether (400 ml.) at a rate sufficient to maintain boiling (moisture excluded). The reactants were stirred for 30 min. after completion of the addition, and water (100 ml.) was dropped in followed by sulphuric acid (800 ml., 10%). Material from the ethereal layer, when distilled, gave 3-phenylbutanol (69·5 g., 93%), b. p. 138°/21 mm.

This (1 ml.) in dry pyridine (5 ml.) was added to 3 : 5-dinitrobenzoyl chloride (1 g.) in dry benzene (10 ml.) and left at room temperature for 18 hr. Thus was obtained 3-*phenylbutyl* 3 : 5-*dinitrobenzoate*, m. p. 73—74° (from alcohol) (Found : C, 59·6; H, 4·6; N, 8·1. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%).

1-*Bromo*-3-*phenylbutane.*—(*a*) This compound, prepared from 3-phenylbutanol by Levene and Marker's method (*loc. cit.*) with phosphorus tribromide, had b. p. 117—118°/14 mm.

(*b*) 3-Phenylbutanol (15 g.) was refluxed with aqueous hydrobromic acid (21 g., 48%) and concentrated sulphuric acid (7 g.) for 3 hr. When cold the heavy bromo-compound was separated, washed with concentrated sulphuric acid (2 ml.), then with water, and dissolved in ether. The ethereal solution, after being washed and dried, was concentrated. The residual oil was fractionated, giving 1-bromo-3-phenylbutane (16 g., 75%), b. p. 127—128°/21 mm. Levene and Marker record b. p. 120°/17 mm. for this compound.

2-*Methyl*-6-*phenylheptan*-3-*ol.*—Approx. one-fifth of a solution of 1-bromo-3-phenylbutane (24·5 g., 1 mol.) in dry ether (30 ml.) was added to magnesium turnings (3 g., 1 mol.) and a few crystals of iodine (moisture excluded). After gentle warming to start the reaction dry ether (60 ml.) was added, followed gradually by the remainder of the ethereal solution of 1-bromo-3-phenylbutane. After 20 min.' boiling the reactants were cooled to 0° and a solution of *iso*butaldehyde (9 g., 1 mol.) in dry ether (25 ml.) was dropped in. After a further hr.' stirring the ethereal solution was poured on ice-water (600 ml.) containing ammonium chloride (40 g.). The ethereal layer was separated and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with water, dried, and concentrated. The residue gave a main fraction (18·1 g., 76·5%), b. p. 132—159°/14 mm. Refractionation of this gave 2-*methyl*-6-*phenylheptan*-3-*ol* (10·6 g.), b. p. 146—150°/12 mm., n_D^{15} 1·5045 (Found : C, 81·6; H, 10·8. $C_{14}H_{22}O$ requires C, 81·5; H, 10·7%).

Attempts to prepare the 3 : 5-dinitrobenzoate, the phenylurethane, and the α-naphthylurethane of 2-methyl-6-phenylheptan-3-ol did not yield solid compounds.

2-*Methyl*-6-*phenylheptan*-3-*one.*—2-Methyl-6-phenylheptan-3-ol (2·1 g.) in benzene (10 ml.) was added gradually to sodium dichromate (1·9 g.) dissolved in sulphuric acid (1·7 g.) and water (10 ml.). When the reaction mixture was cold it was poured into water and extracted with ether. The ethereal extracts gave 2-*methyl*-6-*phenylheptan*-3-*one* (1·3 g., 62%), b. p. 145—146°/12 mm., n_D^{20} 1·4997 (Found : C, 82·0; H, 9·5. $C_{14}H_{20}O$ requires C, 82·3; H, 9·8%). This afforded a 2 : 4-*dinitrophenylhydrazone*, m. p. 89—90° (Found : C, 61·9; H, 6·3; N, 14·8. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

Examination of the Products obtained on the Dehydration of 2-*Methyl*-6-*phenylheptan*-3-*ol.*—The products from the dehydration methods described below were examined by a common method.

A slight excess of ozone was passed into a solution of the products of dehydration in acetic acid. The solution was poured into water and distilled from zinc dust (2 g.). The first three fractions (10 ml.) were each treated with 2 : 4-dinitrophenylhydrazine (0·5 g.) in acetic acid (15 ml.). The resultant 2 : 4-dinitrophenylhydrazones were separated by chromatography from benzene on alumina.

In a trial experiment a benzene solution of acetone 2 : 4-dinitrophenylhydrazone (0·29 g.) and *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·18 g.) was chromatographed on alumina (100 g.). As no separation into bands occurred on development of the chromatogram, isolation of the dinitrophenylhydrazones was achieved by continuous elution with benzene. *iso*Butaldehyde dinitrophenylhydrazone (0·18 g., 100%) was obtained from the first fractions (140 ml.), and acetone dinitrophenylhydrazone (0·24 g., 83%) from the later fractions (280 ml.).

Dehydration of 2-Methyl-6-phenylheptan-3-ol.—(a) 2-Methyl-6-phenylheptan-3-ol (3·2 g.) was heated for 2 hr. with powdered, freshly fused potassium hydrogen sulphate at 150—160°/100 mm. under dry nitrogen. Water distilled off at first, followed by an oil. After cooling, the residue was extracted with ether and the extracts were combined with the distillate. The ethereal solution was washed and dried. The ether was evaporated and the residue distilled under reduced pressure. Redistillation gave a main fraction, b. p. 118—120°/16·5 mm., n_D^{16} 1·5018 (1·8 g., 62%) (Found : C, 89·0; H, 10·5. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%). Two other attempted dehydrations under similar conditions resulted in products which were incompletely dehydrated.

2-Methyl-6-phenylheptan-3-ol (9 g.) was heated for 2 hr. with powdered freshly fused potassium hydrogen sulphate (40 g.) at 150—160°/80 mm. in an atmosphere of nitrogen. The product, isolated as in the previous experiment but not distilled, was heated with fresh potassium hydrogen sulphate (40 g.) under the same conditions for 1½ hr. more. The product isolated as above was separated by distillation into five fractions : (1) (0·5 g.), b. p. 100—118°/16 mm., n_D^{20} 1·5005; (2) (1·5 g.), b. p. 121—124°/16 mm., n_D^{20} 1·5007; (3) (2·85 g.), b. p. 125—128°/16 mm., n_D^{20} 1·5010; (4) (0·55 g.), b. p. 128—130°/16 mm., n_D^{20} 1·5010; (5) (0·5 g.), b. p. 130—135°/16 mm., n_D^{20} 1·5019. Fractions 1—4 (5·4 g., 68%) were combined and part (0·28 g.) was examined by the general method which has been described. The products were *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·025 g.; m. p. 179—180°) and acetone 2 : 4-dinitrophenylhydrazone (0·185 g.; m. p. 118—121°).

(b) *With anhydrous potassium hydrogen sulphate in xylene.* A solution of 2-methyl-6-phenylheptan-3-ol (0·9 g.) in xylene (5 ml.) was boiled under reflux for 18 hr. with potassium hydrogen sulphate (24 g.). The mixture was extracted with ether and the ethereal extracts were washed and dried. The solvents were evaporated by maintaining the residue at 100°/50 mm. The crude heptene (0·55 g.), examined by the general method described, yielded a 2 : 4-dinitrophenylhydrazone (0·31 g.), which on separation gave *iso*butaldehyde 2 : 4-dinitrophenylhydrazone (0·070 g., m. p. 176—179°) and acetone 2 : 4-dinitrophenylhydrazone (0·24 g., m. p. 121—123°).

(c) *With phosphoric oxide in benzene.* 2-Methyl-6-phenylheptan-3-ol (4·1 g.) in dry benzene (25 ml.) was boiled under reflux for 3 hr. with phosphoric oxide (5 g.). There was much frothing and the solid became discoloured. When cold the solution was decanted and the residue treated with water and extracted with ether. The combined benzene and ether solutions were washed, dried, and evaporated. The residue was separated into fractions (1) (0·1 g.), b. p. 40—120°/15 mm., n_D^{15} 1·5090, (2) (0·3 g.), b. p. 120—124°/15 mm., n_D^{15} 1·5110, (3) (1·7 g.), b. p. 125—127°/15 mm., n_D^{15} 1·5131, and (4) (0·45 g.), b. p. 160—230°/16 mm., n_D^{15} 1·5150 $\longrightarrow$ 1·5226. Fractions (2) and (3) (2 g., 50%) contained the heptenes (Found : C, 88·8; H, 11·0%).

Fraction (3) (0·33 g.), examined by the general method, yielded crude 2 : 4-dinitrophenylhydrazones (0·48 g.), a part of which (0·19 g.) was separated by chromatography into acetophenone 2 : 4-dinitrophenylhydrazone (0·06 g.), m. p. 237—240°, mixed m. p. with an authentic specimen (m. p. 244—247°) 237—242°, and acetone 2 : 4-dinitrophenylhydrazone (0·13 g.), m. p. 121—123°.

(d) *With phosphorus oxychloride in pyridine.* A solution of 2-methyl-6-phenylheptan-3-ol (0·74 g.) in pyridine (50 ml.) was boiled under reflux for 3 hr. with phosphorus oxychloride (8 ml.) and then left overnight at room temperature. The solution was poured into ice-water (300 ml.) containing concentrated hydrochloric acid (50 ml.). The oil which separated was dissolved in ether and the ethereal solution washed and evaporated. Part (0·31 g.) of the residual oil (0·62 g.), examined by the usual procedure, gave a 2 : 4-dinitrophenylhydrazone (0·1 g.), which, on purification by chromatography, was shown to be acetone 2 : 4-dinitrophenylhydrazone, m. p. 118—121°. A trace of a 2 : 4-dinitrophenylhydrazone, more soluble in benzene, was obtained from the second fraction obtained by chromatography and this, on further chromatography and recrystallisation from ethanol, was established to be 3-*phenylvaleraldehyde* 2 : 4-*dinitrophenylhydrazone*, m. p. 90—91° (Found : C, 59·2; H, 5·4; N, 16·0. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%).

It is concluded that this dehydration produced 2-methyl-6-phenylhept-2-ene.

Attempted Preparation of 3-*Bromo*-2-*methyl*-6-*phenylheptane*.—Phosphorus tribromide (5 g.) was added to 2-methyl-6-phenylheptan-3-ol (4·2 g.) at 0° and the mixture heated on a steam-bath for an hour. When cold the mixture was poured into ice-water, and the heavy product which separated was dissolved in ether, washed, and dried. Evaporation and distillation gave a main fraction (2·5 g.), b. p. 130—133°/17 mm., n_D^{15} 1·5091 (Found : C, 82·8; H, 9·9; Br, 9·2. Calc. for $C_{14}H_{21}Br$: C, 62·4; H, 7·8; Br, 29·7%). On redistillation the product had an even lower bromine content (Found : C, 88·9; H, 10·4; Br, 3·92%), suggesting that further dehydrobromination had taken place

Preparation of 2-*Methyl*-6-*phenylhept*-2-*ene*.—Dehydrobromination of the bromo-compound (1·7 g.) obtained in the previous experiment was completed by boiling it under reflux in collidine (5 ml.) under nitrogen. After 5 min. collidine hydrobromide had separated. When cold the solution was dissolved in ether and then dried. After evaporation collidine (5 ml.) was added to the residue and the solution boiled under reflux (nitrogen) for 2 hr. When cold, the collidine solution was treated as before. The residue (1·3 g.) was fractionated, giving 2-*methyl*-6-*phenylhept*-2-*ene* (1·1 g.), b. p. 117—119°/12 mm., n_D^{20} 1·5020 (Found : C, 89·6; H, 10·6. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%). The product was examined in the usual way and the resulting 2 : 4-dinitrophenylhydrazones were separated into acetone 2 : 4-dinitrophenylhydrazone (m. p. 121—123°), and 3-phenylvaleraldehyde 2 : 4-dinitrophenylhydrazone which after recrystallisation from ethanol had m. p. 93—94°, undepressed on admixture with the compound prepared previously.

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