134. *β-Alkylation of Certain Kationoid Systems by Means of Grignard Reagents.*

By A. J. Birch and Sir Robert Robinson.

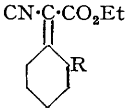
We are interested in the *β*-alkylation of *αβ*-unsaturated ketones and the like in connexion with the synthesis of long-chain aliphatic compounds containing a quaternary carbon atom (cf. J., 1942, 488) and as a means of introduction of the angle-methyl group of substances analogous to the sterols A few typical cases have been examined in order to estimate the scope of the reaction in relation to our problems.

It is well known that the anionoid alkyl of a Grignard reagent often attacks the β-position of a double bond conjugated with a carbonyl, cyano-, or carbethoxyl group, but these groups can also enter into reaction, and the products formed vary with the conditions and even slight variations in structure (cf. Colonge, *Bull. Soc. chim.*, 1935, **2**, 754; 1936, **3**, 413). A possible cause of otherwise inexplicable contrasts which are recorded in the literature of the subject was revealed when Kharasch and Tawney (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) demonstrated the important part played by traces of certain metal ions. It was found that the keto-group of *iso*phorone was normally the site of reaction (cf. Whitmore and Pedlow, *ibid.*, p. 758) but that in the presence of cuprous chloride, addition to the double bond predominated. We have found that carvone behaves similarly, since methylmagnesium iodide, in the presence of cuprous bromide, added almost exclusively to the endocyclic double bond, although Rupe and Liechtenhan (*Ber.*, 1906, **39**, 1122) and Klages (*ibid.*, p. 2310) found that the keto-group was attacked under the usual conditions.

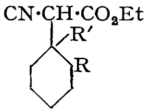
Applying this reaction to 2-keto-$\Delta^{1:9}$-octalin, we obtained a 60% yield of *cis*-2-keto-9-methyldecalin. The configuration of the product was determined by the fact that it gave a homogeneous, crystalline oxime in more than 90% yield and the ketone was oxidised to *cis*-1-methyl*cyclo*hexane-1 : 2-diacetic acid, an authentic sample of which was kindly supplied by Dr. A. L. Walpole. This synthesis is more convenient than that of Linstead, Millidge, and Walpole (J., 1937, 1140) and constitutes a model for possible applications in the steroid field; owing to the production of the *cis*-configuration it is perhaps of greater potential value in relation to the polyterpenes.

It appeared that *trans*-junction of the rings might result from the steric effect of a group, such as carbethoxyl, in position 10, which might subsequently be removed. The presence of such a group would also be expected to oppose the addition, and in order to see if it would still proceed, the action of methylmagnesium iodide, in the presence of cuprous bromide, on 2-keto-10-methyl-$\Delta^{1:9}$-octalin was examined. The ketonic product was isolated as *semicarbazone*, hydrolysis of which gave a substance which may be trans-2-*keto*-9 : 10-*dimethyldecalin*; the rather indefinite melting point indicated that it was not stereochemically homogeneous and the yield was unsatisfactory.

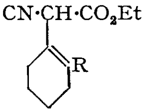
In the hope of obtaining intermediates which might be cyclised to *trans*-decalins or hydrindanes with a keto- or carboxyl group in the 1-position, required for projected steroid syntheses, attention was turned to the action of Grignard reagents on alkylidene cyanoacetic esters. Dialkylated cyanoacetic esters do not react with the Grignard reagents, so side reactions with the ester and cyano-groups should be avoidable. Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 352) have added Grignard reagents to the double bond in compounds of the type of benzylidenecyanoacetic ester, so it seemed highly probable that they would add to compounds of type (I). In fact, (I, R = H) added both *n*-decylmagnesium bromide and methylmagnesium iodide, giving (II; R = H, R′ = $C_{10}H_{21}$, Me). The product of the latter reaction was hydrolysed by means of aqueous alkali to the malonamic acid, which was decarboxylated to 1-*methyl*cyclo*hexane*-1-*acetamide.* The yields in these two cases were 14% and 45% respectively and with (I, R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) the alkylation did not occur. The cause of the low yields was the isomerisation of (I) to (III), a type of transposition which is well known to be favoured by the alicyclic structure. In open-chain compounds the method may be more serviceable.



(I.)



(II.)



(III.)

EXPERIMENTAL.

6-*Methylcarvomenthone.*—A solution of carvone (15·2 g.) in ether (40 c.c.) was slowly added to a stirred and ice-cooled Grignard solution from methyl iodide (16 g.) and magnesium (2·4 g.), containing cuprous bromide (0·1 g.). The mixture was refluxed for 10 minutes. The isolated product was heated with a crystal of iodine for 15 minutes at 180°, cooled, and, after removal of the trace of water, distilled, giving 2·5 g., b. p. *ca.* 200°, probably diene, and 11 g., b. p. 235—240° (Found: C, 79·1; H, 10·5. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

cis-2-*Keto*-9-*methyldecalin.*—2-Keto-$\Delta^{1:9}$-octalin (12 g.) was added to an ice-cooled and stirred Grignard solution (3 g. of magnesium and 19·5 g. of methyl iodide) containing cuprous bromide (0·2 g.). After an hour at room temperature the solution was refluxed for 15 minutes. It was decomposed with ice and dilute hydrochloric acid, and the ethereal layer separated and shaken with saturated aqueous sodium bisulphite for 3 hours. The liquid was filtered, and the solid washed with ether. The combined crystals and aqueous layer were acidified with hydrochloric acid, and heated on the steam-bath under reflux for 30 minutes. The product was a colourless oil with a pleasant camphoraceous odour, b. p. 250—254°, m. p. *ca.* 14·5° (Linstead *et al.*, 17—18°) (Found: C, 79·1; H, 10·7. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

The residue from the bisulphite extraction was distilled with a crystal of iodine, water being produced; on drying and redistillation 2·1 g. of an oil, b. p. 225°, were obtained. This is probably the diene, but was not further examined.

The ketone gave a semicarbazone, m. p. 212—213° (*ex* alcohol) (Linstead *et al.*, 211—212°), a 2 : 4-*dinitrophenylhydrazone*, pale orange needles from alcohol, m. p. 106° (Found: N, 16·8. $C_{17}H_{22}O_4N_4$ requires N, 16·2%), and a *benzylidene* derivative, pale yellow prisms from alcohol, m. p. 85—86° (Found: C, 84·2; H, 8·6. $C_{18}H_{22}O$ requires C, 85·0; H, 8·6%). The ketone (5 g.) gave the oxime (4·6 g.) as colourless prisms from alcohol, m. p. 109°; the mixture of isomerides at first produced was transformed into this variety after contact with aqueous alcoholic hydroxylamine hydrochloride for a week.

Oxidation with nitric acid by the method of Linstead *et al.* gave an acid, m. p. 192°, undepressed by admixture with an authentic specimen of *cis*-1-methyl*cyclo*hexane-1 : 2-diacetic acid, m. p. 192°.

2-*Keto*-9 : 10-*dimethyldecalin.*—2-Keto-10-methyl-$\Delta^{1:9}$-octalin (2·4 g.) in ether (15 c.c.) was slowly added to an ice-cooled and stirred Grignard solution from magnesium (0·5 g.) and methyl iodide (3·0 g.) in ether (20 c.c.), containing cuprous bromide (0·05 g.). After refluxing for 15 minutes the product was isolated and converted into a *semicarbazone*, which recrystallised from alcohol in colourless prisms, m. p. 202—203° (Found: C, 65·5; H, 9·5. $C_{13}H_{23}ON_3$ requires C, 65·9; H, 9·7%); yield, 120 mg. Steam distillation with dilute hydrochloric acid gave colourless prisms with a sweet camphoraceous odour, m. p. 90—95° (Found: C, 79·2; H, 10·9. $C_{12}H_{20}O$ requires C, 80·0; H, 11·1%).

Ethyl 1-n-*Decyl*cyclo*hexane*-1-*cyanoacetate.*—A Grignard solution from *n*-decyl bromide (25 g.) and magnesium (3 g.) in ether (40 c.c.) was slowly added to one of ethyl *cyclo*hexylidenecyanoacetate (15 g.) in ether (40 c.c.) with stirring and ice-cooling. After ½ hour the mixture was refluxed for 15 minutes. The product was isolated in the known manner and distilled. Following a fraction consisting of decane and unchanged ester, material, b. p. 200—235°/15 mm., was collected. On addition of alcohol eicosane was precipitated and collected. After removal of the solvent a pale yellow oil, b. p. 230—235°/15 mm., was obtained (yield, 14%) (Found: C, 75·1; H, 11·0. $C_{21}H_{37}O_2N$ requires C, 75·2; H, 11·0%).

Ethyl 1-*Methyl*cyclo*hexane*-1-*cyanoacetate.*—Ethyl *cyclo*hexylidenecyanoacetate (24 g.) in ether (50 c.c.) was brought into reaction as above with a Grignard solution from methyl iodide (19·5 g.) and magnesium (3 g.), but before distillation unchanged material was removed by treatment with an excess of cold aqueous alcoholic sodium cyanide for 1 hour. The *product* was an almost colourless oil, b. p. 155—160°/12 mm. (Found: C, 68·7; H, 9·0. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1%); yield, 45%.

1-*Methyl*cyclo*hexane*-1-*acetamide.*—The above ester (5 g.) was refluxed with 15% aqueous sodium hydroxide for 3 hours, and the solution acidified. The precipitated acid (2·8 g.) crystallised from aqueous alcohol in plates, m. p. 151° (Found: C, 60·3; H, 8·4. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·5%). This 1-*methyl*cyclo*hexane*-1-*malonamic acid*, when heated at 180° for 20 minutes, afforded a neutral *product*, which crystallised from alcohol in flat needles, m. p. 112—113° (Found: C, 69·3; H, 11·3. $C_9H_{17}ON$ requires C, 69·6; H, 11·0%).

Ethyl 2-β-*Carbethoxyethyl*-Δ^1-cyclo*hexene*-1-*cyanoacetate.*—A mixture of 2-β-carbethoxyethyl*cyclo*hexanone (9·9 g.), ethyl cyanoacetate (5·7 g.), and piperidine (3 drops) was heated on the steam-bath for 10 hours. Some unchanged ester and 5 g. of an oil, b. p. 150—153°/0·1 mm. (Found: C, 65·7; H, 8·1. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·9%), were obtained.

After treatment with methylmagnesium iodide as above, the substance reacted almost completely with aqueous alcoholic sodium cyanide to give the water-soluble addition compound, so the double bond appears to be endo- rather than exo-cyclic.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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