189. *The Action of Grignard Reagents on 4-Diphenylyl Piperidinomethyl Ketone and on* N-*Methylcinchotoxine.*

By (Miss) B. R. Carpenter and E. E. Turner.

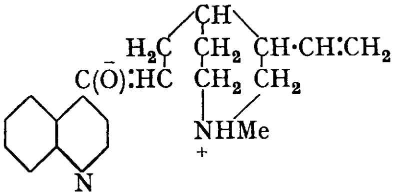
Henley and Turner (J., 1931, 1182) showed that the carbonyl group in 1-phenacylpiperidine reacted normally with ten different Grignard reagents, but abnormally with *n*-hexyl-, *n*-heptyl-, and *cyclo*hexyl-magnesium halides. Compounds of the type $R{\cdot}CO{\cdot}CH_2 \ldots NR'_2$ are capable of two kinds of reaction with Grignard reagents, *viz.*, (*a*) and (*b*) :

$$\begin{tikzcd}
R{\cdot}CO{\cdot}CH_2 \ldots NR'_2 \arrow[r, "R''MgX", "(a)"'] \arrow[d, shift left] & R{\cdot}CR''(OH){\cdot}CH_2 \ldots NR'_2 \\
R{\cdot}C(\overset{-}{O}){:}CH \ldots \overset{+}{N}HR'_2 \arrow[r, "R''MgX", "(b)"'] \arrow[u, shift left] & R{\cdot}C(OMgX){:}CH \ldots NR'_2 + R''H.
\end{tikzcd}$$

The previous work thus supplies ten examples of (*a*) and three of (*b*), the latter apparently being caused by the properties of R″. In general, whether (*a*) or (*b*) preponderates will depend on the nature of R, R′, and R″.

4-*Diphenylyl piperidinomethyl ketone*, $C_6H_5\cdot C_6H_4\cdot CO\cdot CH_2\cdot NC_5H_{10}$, reacts with methylmagnesium iodide (present in large excess) to give the original material (*b*) and 4-*diphenylylmethylpiperidinomethylcarbinol*, $C_6H_5\cdot C_6H_4\cdot CMe(OH)\cdot CH_2\cdot NC_5H_{10}$, but, with phenylmagnesium bromide, the vigorous reaction which occurs takes course (*b*) to the exclusion of (*a*).

N-Methylcinchotoxine was caused to react with the same pair of Grignard reagents under a variety of different conditions. On no occasion was any reaction of type (*a*) observed, so *N*-methylcinchotoxine tends to avoid the usually accepted ketonic formula and to react in accordance with the annexed structure, a point of some interest in connexion with the physiological action of this base, which is thus formally a betaine.



Comanducci (*Boll. Chim. Farm.*, 1907, **46**, 752; *Rend. Accad. Sci. Fis. Mat. Napoli*, 1909, **3**, 15, 32, 240) stated that by the action of Grignard reagents on cinchotoxine itself he obtained a number of "cinchotoxols," in which the ·CO· group had been converted into ·CR(OH)· (R = Et, Ph, and α-$C_{10}H_7$). It is surprising that cinchotoxine, containing a free imino-group, should react, and that its *N*-methyl derivative should not.

4-Diphenylyl piperidinomethyl ketone was prepared by the action of piperidine on 4-diphenylyl bromomethyl ketone. The latter substance was accumulated during a study of the bromination of 4-diphenylyl methyl ketone, and was obtained by other workers whilst this investigation was in progress. Drake and Bronitsky (*J. Amer. Chem. Soc.*, 1930, **52**, 3715) brominated the ketone in acetic acid solution, and obtained a product, m. p. 125·5°, whilst John (*J. pr. Chem.*, 1932, **133**, 259) performed the same reaction using artificial irradiation and recorded m. p. 95°. We find that when bromine and the ketone in exactly equimolecular proportion react in glacial acetic acid solution, bromination to the extent of more than 95% occurs in the side chain and none in the 4′-position. The bromo-ketone obtained, m. p. 126—127°, is identical with the product of a Friedel–Crafts condensation between bromoacetyl bromide and diphenyl, and is different from 4′-*bromo*-4-*diphenylyl methyl ketone*, m. p. 131°, formed by condensing acetyl chloride with 4-bromodiphenyl.

Monobromination of 4-diphenylyl *iso*propyl ketone and of 4-diphenylyl *iso*butyl ketone also occurs entirely in the side chain.

The hydrochlorides of several of the bases mentioned in this paper were tested for antimalarial activity, but none was detected.

EXPERIMENTAL.

4-*Diphenylyl Bromomethyl Ketone.*—Anhydrous aluminium chloride (1·2 mols.) was added gradually to a mixture of diphenyl (2 mols.), bromoacetyl bromide (36 g.; 1 mol.), and carbon disulphide (20 c.c.). The initial vigorous reaction slackened after ½ hour, and the mixture was then kept in hot water for 2 hours. Decomposition, completed with hot water so as to remove all solvent, gave a product which, after being air-dried, was dissolved in the minimum quantity of boiling toluene. On cooling, 41 g. of product, m. p. 124—125°, separated. Recrystallisation from alcohol or light petroleum (b. p. 80—100°) raised the m. p. to 126—127° (37·5 g.; 76% yield).

The percentage of labile bromine in this and all similar compounds was determined by heating about 0·25 g. of material with about 2·5 c.c. of piperidine in a sealed glass tube for 1 hour at 100°. The contents of the tube were washed out with alcohol, water added, and Br′ determined as AgBr (Found: Br, 29·0, 28·9. Calc.: Br, 29·0%).

The bromo-compound combined readily with dimethylaniline at 100° to give *phenyl*-4-*phenylphenacyldimethylammonium bromide*, which, crystallised from methyl alcohol–ether and then from water, formed slender needles, m. p. 144—145° (Found: Br, 20·4. $C_{22}H_{22}ONBr$ requires Br, 20·1%).

Bromination of 4-*Diphenylyl Methyl Ketone.*—(a) *Qualitatively.* Bromine (3 c.c.), dissolved in 20 c.c. of glacial acetic acid, was added gradually to a solution of the ketone (10 g.) in 100 c.c.

of the same solvent, at 50°. The initial reaction took a few minutes to begin, but was then very rapid. Addition of water gave 13 g. of leaflets, m. p. 124—126° after one crystallisation from alcohol and 126—127° after a second crystallisation from toluene.

(b) *Quantitatively.* A similar procedure was adopted, except that the ketone and the bromine were weighed to ± 0·01 g. The total crude bromination product, obtained by pouring the acetic acid solution into a large bulk of water, filtering, and vacuum-drying, weighed 4·75 g. (calc. for monobromination, 4·91 g.), and had m. p. 113—121° (Found : total Br, 28·7, 28·6; labile Br, 28·6, 28·7%).

4'-*Bromo*-4-*diphenylyl Methyl Ketone.*—Anhydrous aluminium chloride (9 g.) was added gradually to a solution of acetyl chloride (7 g.) and 4-bromodiphenyl (13 g.) in 15 c.c. of carbon disulphide. The first reaction over, the mixture was kept in warm water for ½ hour and then decomposed. The crude *ketone* (yield, 98%) crystallised from alcohol or from light petroleum (b. p. 80—100°) in long thin plates, m. p. 131°, or, mixed with 4-diphenylyl bromomethyl ketone, 95—105° (Found : Br, 28·7. $C_{14}H_{11}OBr$ requires Br, 29·0%).

Bromination of 4-*Diphenylyl* iso*Propyl Ketone.*—The ketone was prepared from diphenyl, *iso*butyryl chloride, aluminium chloride, and carbon disulphide, and, after being crystallised several times from light petroleum (b. p. 40—60°), had m. p. 61—62°. Willgerodt and Scholtz (*J. pr. Chem.*, 1910, ii, **81**, 400), who incorrectly described the ketone as the 3-derivative, gave m. p. 56° (Found : C, 85·2; H, 7·2. Calc. : C, 85·7; H, 7·2%). The p-*nitrophenylhydrazone* formed golden needles, m. p. 143—144°, from butyl alcohol (Found : N, 12·0. $C_{22}H_{21}O_2N_3$ requires N, 11·7%).

Bromination of 5·60 g. of the ketone under quantitative conditions gave, in two different experiments, 7·00 and 7·30 g. of crude bromo-derivative (calc. for monobromination, 7·57 g.). The first product had m. p. 92—100°, and contained total Br, 26·4, labile Br, 26·6%; the second had m. p. 91—100° and contained total Br, 26·5, labile Br, 26·6% (Calc. for monobromination in side-chain, Br, 26·4%). Recrystallisation of the crude bromination product gave a substance, m. p. 99—100°.

4-*Diphenylyl α-Bromo*iso*propyl Ketone.*—α-Bromo*iso*butyryl bromide, diphenyl, aluminium chloride, and carbon disulphide gave the *bromo-ketone*, which after being crystallised from the least possible amount of toluene and then from alcohol, formed plates, m. p. 99—100° (Found : Br, 26·4. $C_{16}H_{15}OBr$ requires Br, 26·4%).

Bromination of 4-*Diphenylyl* iso*Butyl Ketone.*—The ketone prepared from diphenyl, *iso*valeryl chloride, etc., had m. p. 77—78°, not 63° as recorded by Willgerodt and Scholtz (*loc. cit.*), who regarded the ketone as the 3-derivative (Found : C, 85·3; H, 7·5. Calc. : C, 85·7; H, 7·6%).

Quantitative bromination of 5·90 g. of the ketone gave : 1*st Expt.* Yield, 7·20 g. (calc. for monobromination, 7·80 g.); m. p. 127—131°. Total Br, 25·2; labile Br, 25·1%. 2*nd Expt.* Yield, 7·50 g.; m. p. 126—130°. Total Br, 25·2; labile Br, 25·2%. Crystallisation of the crude product raised the m. p. to 131—132°.

4-*Diphenylyl α-Bromo*iso*butyl Ketone.*—This substance, prepared from α-bromo*iso*valeryl bromide, was crystallised from toluene and then from light petroleum (b. p. 80—100°). It formed needles, m. p. 131—132° (Found : Br, 25·1. $C_{17}H_{17}OBr$ requires Br, 25·15%).

4-*Phenylacetyl*-4'-*acetyldiphenyl* was prepared from phenylacetyl chloride, 4-diphenylyl methyl ketone, and aluminium chloride. After being crystallised successively from butyl alcohol and ethyl alcohol, it formed slender needles, m. p. 118—119° (Found : C, 84·8; H, 6·1. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·8%).

Phenyl 4-*Diphenylyl Ketone.*—Nenitzescu, Isacescu, and Ionescu (*Annalen*, 1931, **491**, 210) state that this substance is formed when diphenyl and benzoyl chloride are boiled together. We find that no interaction occurs in absence of a catalyst. Using aluminium chloride, we obtained a yield of 62%.

Phenyl-4-*diphenylylmethylcarbinol.*—(a) The last-named ketone reacted readily with methylmagnesium iodide (3 mols.) to give a 94% yield of the crude *carbinol*, m. p. 99—100°. This crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 102—103° (Found : C, 86·9; H, 6·6. $C_{20}H_{18}O$ requires C, 87·6; H, 6·6%). (b) 4-Diphenylyl methyl ketone and 5 mols. of phenylmagnesium bromide gave a 50% yield of pure carbinol, m. p. 102—103°, alone or when mixed with the product from (a).

4-*Diphenylylmethyl*iso*propylcarbinol*, obtained from 4-diphenylyl methyl ketone and *iso*propylmagnesium bromide or from 4-diphenylyl *iso*propyl ketone and methylmagnesium iodide, crystallised from light petroleum (b. p. 60—80) in plates, m. p. 63—64° (Found : C, 84·3; H, 8·3. $C_{17}H_{20}O$ requires C, 85·0; H, 8·4%).

4 : 4'-*Bischloroacetyldiphenyl.*—Diphenyl (1 mol.), chloroacetyl chloride (2·5 mols.), and

aluminium chloride (3 mols.) were allowed to react in presence of carbon disulphide. The product obtained by decomposition with water and acid crystallised from *cyclo*hexanone in large irregular needles, m. p. 226—227° (Found: Cl, 22·4. $C_{16}H_{12}O_2Cl_2$ requires Cl, 23·1%).

4 : 4'-*Bispiperidinoacetyldiphenyl*.—The bischloro-compound was added gradually to 4 parts of piperidine, with good stirring. The paste obtained was ground from time to time, and after an hour was diluted with water and dissolved in hydrochloric acid. The solution was filtered, treated with excess of ammonia, and the solid was collected and dried. It then separated from dilute acetone as a brownish-yellow crystalline powder, m. p. 143—144° (Found: N, 6·8. $C_{26}H_{32}O_2N_2$ requires N, 6·9%).

4-*Diphenylyl Piperidinomethyl Ketone*.—4-Diphenylyl bromomethyl ketone was treated with piperidine in the manner just described. The *compound* crystallised from absolute alcohol in slender needles, m. p. 93—94° (Found: N, 5·1. $C_{19}H_{21}ON$ requires N, 5·0%). The *methiodide*, obtained by heating the components at 100°, crystallised from water in plates, m. p. 184—185° (Found: I, 30·0. $C_{20}H_{24}ONI$ requires I, 30·0%).

4-*Diphenylylmethylpiperidinomethylcarbinol*.—4-Diphenylyl piperidinomethyl ketone (1 mol.) was gradually added to a Grignard reagent prepared from 10 mols. of methyl iodide and 20 ats. of magnesium (decanted before use). The solution obtained was boiled for 2 hours, left overnight, and then decomposed with water and dilute hydrochloric acid. The oily solid was separated and dissolved in hot alcohol. On cooling, the hydrochloride of the original base separated. The mother-liquor from the latter was treated with ammonia, and the precipitated solid *carbinol* dried in a vacuum. It crystallised from absolute alcohol in slender needles, m. p. 89—90° (Found: N, 4·9. $C_{20}H_{25}ON$ requires N, 4·7%). The *methiodide*, readily formed at 100°, crystallised from water in plates, m. p. 186—187° (Found: I, 28·8. $C_{21}H_{28}ONI$ requires I, 29·0%). A mixture of this methiodide with that (m. p. 184—185°) of the ketone melted indefinitely at 170—180°.

Cinchonine Methobromide.—The following is a much more convenient method of preparation than that of passing methyl bromide into a methyl-alcoholic suspension of the alkaloid. Cinchonine (45 g.) was suspended in 450 c.c. of absolute methyl alcohol and 14·5 c.c. of methyl sulphate were added. The quickly-formed solution was gently warmed for ½ hour, and the solvent was then removed rapidly under diminished pressure. The residual methosulphate was sometimes a honey-like syrup and sometimes a mass of needles. It was dissolved in 500 c.c. of water, the solution freed from traces of cinchonine by filtration, warmed to about 60°, and treated with a solution of 36 g. of potassium bromide in 400 c.c. of boiling water. On cooling, 40 g. of pure cinchonine methobromide separated.

The methobromide was converted into *N*-methylcinchotoxine by the method of Claus and Miller (*Ber.*, 1880, **13**, 2290). The preparation of the toxine *via* the methiodide (Rabe and Ritter, *Ber.*, 1905, **38**, 2771) was in every respect less satisfactory.

Action of Grignard Reagents on N-*Methylcinchotoxine*.—(a) *Methylmagnesium iodide*. The base was added gradually to the Grignard reagent (6 mols.), and thereafter the solution was boiled for 6 hours. Aqueous ammonium chloride was added, and the ethereal solution separated, dried over potassium carbonate, and evaporated. After being crystallised from light petroleum (b. p. 60—80°), the residue had m. p. 72—73°, alone or when mixed with the original base (m. p. 72—73°). The latter had $[\alpha]_{5791}^{20^\circ} + 19{\cdot}9^\circ$ in chloroform, whilst the product obtained from the Grignard reaction had $[\alpha]_{5791}^{20^\circ} + 20{\cdot}0^\circ$.

When the latter product was kept in alcoholic methyl iodide solution, the methiodide separated in warty crystalline masses, which, after crystallisation from absolute alcohol, melted at 196—197°, alone or when mixed with *N*-methylcinchotoxine methiodide, m. p. 196—197°.

(b) *Phenylmagnesium bromide*. Ten mols. of this reagent were used. The product, after being crystallised from light petroleum, had m. p. 72—73°. A mixture of *N*-methylcinchotoxine with both the Grignard products (a) and (b) melted at 72—73°.

The authors thank the Department of Scientific and Industrial Research (Chemotherapy Committee of the Medical Research Council) for a grant.

BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, April* 19*th*, 1934.]