127. *The Chemistry of the Pyrrocolines. Part V. The Action of Grignard Reagents and of Iodine on 3-Acetyl-2-phenylpyrrocoline.*

By E. T. Borrows and D. O. Holland.

When acted upon by a Grignard reagent, 3-acetyl-2-phenylpyrrocoline forms a magnesium complex which on hydrolysis yields 2-phenylpyrrocoline and a methyl ketone.

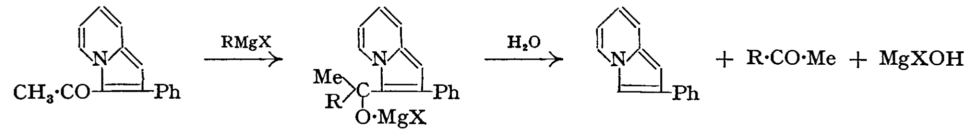
By the action of iodine, 3-acetyl-2-phenylpyrrocoline is converted into 1-iodo-3-acetyl-2-phenylpyrrocoline and 1 : 3-di-iodo-2-phenylpyrrocoline.

Two projected syntheses of 1-acetyl-2-phenylpyrrocoline failed owing to unexpected loss, at ring closure stage, of an acetyl or a hydroxethyl group resulting in the formation of 2-phenylpyrrocoline.

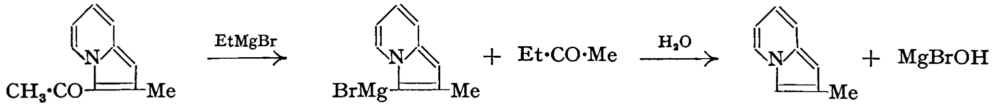
With the object of introducing substituents into the 3-position of the pyrrole ring in pyrrocoline, the action of various Grignard reagents on 3-acetyl-2-phenylpyrrocoline has been investigated.

Preliminary trials having shown that some acetyl compound escaped reaction when less than 1·5 mols. of the Grignard reagent were employed, this proportion was used in all subsequent experiments.

In each case the additive organo-metallic complex was isolated and failed to give a positive indication of the presence of a carbon–metal linkage (Gilman and Schultz, *J. Amer. Chem. Soc.*, 1925, **47**, 2002). On hydrolysis, the complexes yielded 2-phenylpyrrocoline and the appropriate ketone, Me·CO·R; no ketone could be isolated from the unhydrolysed complex. The reaction may therefore be formulated :



Whilst these results are in harmony with that obtained by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Zentr.*, 1936, **107**, ii, 2910), who showed that methyl ethyl ketone is produced when ethylmagnesium bromide reacts with 3-acetyl-2-methylpyrrocoline, they are not in agreement with the suggestion of these authors that the reaction takes the course :



Numerous attempts to isolate tertiary alcohols corresponding to (II) in the form of their acetates or benzoates were unsuccessful, and when benzoyl chloride was employed for this purpose 3-benzoyl-2-phenylpyrrocoline was obtained; this is not surprising in view of the ease of benzoylation of 2-phenylpyrrocoline (cf. Part I, *J.*, 1946, 1069).

Extension of the reaction by allowing methylmagnesium iodide and ethylmagnesium bromide to react with 3-benzoyl-2-phenylpyrrocoline resulted in the formation of metallic complexes which gave no positive indication of the presence of carbon–magnesium linkages and on hydrolysis regenerated the original 3-benzoyl compound as the principal product. It seems likely, therefore, that these metallic complexes are co-ordinate compounds of the type $>C=O-MgRX$. Such complexes are known to undergo intramolecular rearrangement in the presence of excess of Grignard reagent to the tertiary alcohol derivative (cf. Gilman and Jones, *J. Amer. Chem. Soc.*, 1946, **32**, 1243), and presumably this occurs to a certain extent in the above two experiments, for hydrolysis of the filtrates from the reactions gave 2-phenylpyrrocoline and the ketone (Me·CO·Ph or Et·CO·Ph).

As an alternative approach to the preparation of organo-metallic derivatives of substituted pyrrocolines, the action of iodine on 3-acetyl-2-phenylpyrrocoline was investigated. In alcoholic solution this resulted in the production of 1 : 3-*di-iodo-2-phenylpyrrocoline*, whilst in the presence of sodium acetate, to prevent hydrolysis of the acetyl group, 1-*iodo*-3-*acetyl*-2-*phenylpyrrocoline* was obtained.

Each of these iodo-compounds yielded α-picolinic acid *N*-oxide and benzoic acid on oxidation. Attempts to deacetylate 1-iodo-3-acetyl-2-phenylpyrrocoline, with a view to obtaining an iodo-compound suitable for the preparation of a Grignard reagent, proved unsuccessful since loss of iodine occurred before hydrolysis was complete.

An effort was made to extend these reactions to 1-acetyl-2-phenylpyrrocoline but the following two attempted syntheses of this compound were unsuccessful owing to the unexpected removal of an acetyl or a hydroxyethyl group during ring closure :

(i) 2-(2-Hydroxypropyl)pyridine combined readily with phenacyl bromide. The resultant phenacyl-2-(2-hydroxypropyl)pyridinium bromide, which was characterised as a *chloroplatinate*, on treatment with alkali underwent a retrograde aldol condensation and gave only 2-phenylpyrrocoline.

(ii) Interaction of 2-(2-ketopropyl)pyridine and phenacyl bromide gave little quaternary product, and from the crude reaction mixtures small quantities of 2-phenylpyrrocoline were isolated directly without recourse to alkaline treatment for ring closure.

EXPERIMENTAL.

(All m. ps. are uncorrected.)

Action of Grignard Reagents on 3-Acetyl-2-phenylpyrrocoline.—(*a*) A solution of the acetyl compound (8 g.) in ether (25 c.c.) was added dropwise to a solution of ethylmagnesium bromide (1·5 mols.) in ether and the stirring continued for an additional 25 minutes. The resulting buff-coloured *solid* was filtered off and washed with ether (Found : N, 3·8; Br, 21·8; Mg, 6·8. $C_{18}H_{18}ONBrMg$ requires N, 3·8; Br, 21·7; Mg, 7·3%).

The combined filtrates and washings were evaporated to dryness. *iso*Propyl alcohol (10 c.c.) was added and the distillation continued; the distillate gave no precipitate with Brady's 2 : 4-dinitrophenylhydrazine reagent, but the residue, after hydrolysis with water, yielded 2-phenylpyrrocoline (0·74 g.) and a trace of methyl ethyl ketone isolated as its 2 : 4-dinitrophenylhydrazone.

The buff-coloured complex (13·44 g.) is soluble in chloroform, alcohol, pyridine, and dimethylaniline, and in the two last solvents gave a negative reaction in the Gilman and Schultz test (*loc. cit.*). On decomposition with water it yielded 2-phenylpyrrocoline (4·05 g.; 62%) and methyl ethyl ketone isolated as its 2 : 4-dinitrophenylhydrazone (1·76 g.), m. p. 114°, alone and mixed with an authentic specimen.

The complex appeared to be stable, and its alcoholic solution with picric acid gave 2-phenylpyrrocoline picrate, m. p. 161°, alone and mixed with an authentic specimen.

(*b*) When phenylmagnesium bromide (or iodide) or phenyl-lithium was used instead of ethylmagnesium bromide, parallel results (and yields) were obtained, and the reàction was not notably modified when the Grignard reagent was added to the acetyl compound or when benzene was used as solvent instead of ether. The liberated acetophenone gave a 2 : 4-dinitrophenylhydrazone, m. p. 237°, alone and mixed with an authentic specimen.

Action of Grignard Reagents on 3-*Benzoyl*-2-*phenylpyrrocoline*.—A solution of the benzoyl compound (6·65 g.) in benzene (50 c.c.) was slowly added to a solution of methylmagnesium iodide (1·5 mols.) in benzene (25 c.c.) and ether (5 c.c.), and, after 30 minutes, the yellow material (7·75 g.) was filtered off and washed with benzene. On hydrolysis with water it yielded unchanged 3-benzoyl-2-phenylpyrrocoline (4·9 g.; 74%). From the benzene filtrate, after shaking with water, there was isolated 2-phenylpyrrocoline (0·61 g.; 15%) and acetophenone (0·24 g.).

A parallel result was obtained when ethylmagnesium bromide was used instead of methylmagnesium iodide.

1 : 3-*Di-iodo*-2-*phenylpyrrocoline Hydriodide*.—A solution of 3-acetyl-2-phenylpyrrocoline (2·35 g.) and iodine (2·54 g.) in absolute alcohol (60 c.c.) was heated under reflux for an hour. The red needle-like product (2·8 g.) which had separated was removed by filtration and crystallised from methyl cyanide (100 c.c.); 1 : 3-*di-iodo*-2-*phenylpyrrocoline hydriodide* was thus obtained as iridescent bronze platelets (2·3 g.), m. p. 203° (decomp.) (Found : C, 29·3; H, 2·3; N, 2·4; I, 66·4; active H, 0·17. $C_{14}H_9NI_2,HI$ requires C, 29·3; H, 1·7; N, 2·4; I, 66·5; active H, 0·17%).

1-*Iodo*-3-*acetyl*-2-*phenylpyrrocoline*.—A solution of 3-acetyl-2-phenylpyrrocoline (0·5 g.), anhydrous sodium acetate (0·1 g.), and iodine (0·5 g.) in absolute alcohol (15 c.c.) was heated under reflux for 2 hours, concentrated, diluted with water, and extracted with ether. The 1-*iodo*-3-*acetyl*-2-*phenylpyrrocoline* separated from aqueous alcohol in yellow needles, m. p. 114—116° (0·48 g.; 63%) (Found : C, 53·3; H, 3·4; N, 3·8; I, 34·7. $C_{16}H_{12}ONI$ requires C, 53·2; H, 3·3; N, 3·9; I, 35·2%).

1 : 3-Diacetyl-2-phenylpyrrocoline, submitted to similar treatment, was recovered unchanged.

1-*Phenacyl*-2-(2-*hydroxypropyl*)*pyridinium Choroplatinate*.—A mixture of phenacyl bromide (4·4 g.) and 2-(2-hydroxypropyl)pyridine (3 g.) (*Org. Synth.*, 1943, **23**, 83) was warmed, and the vigorous reaction which followed was moderated by cooling; after 24 hours the quaternary salt had set to a non-crystallisable hard yellow glass.

A portion (0·82 g.) of this material yielded, in the usual way, 1-*phenacyl*-2-(2-*hydroxypropyl*)*pyridinium choroplatinate*, a buff-coloured powder (1·01 g.), m. p. 225° (decomp.), depressed on admixture with 1-phenacyl-2-methylpyridinium chloroplatinate of m. p. 232° (decomp.) (Found : C, 41·9; H, 4·3; N, 3·1; Pt, 21·7. $C_{32}H_{36}O_4N_2Cl_6Pt$ requires C, 41·8; H, 3·9; N, 3·05; Pt, 21·2%).

The yield of the choroplatinate was equivalent to a 90% production of the original quaternary ammonium bromide.

A solution of the quaternary ammonium bromide (1·9 g.) in water (40 c.c.) was decomposed with sodium bicarbonate, but the only crystalline product which could be isolated from the reaction mixture was 2-phenylpyrrocoline (0·5 g.), m. p. 214° (decomp.) (Found : N, 7·0. Calc. : N, 7·25%). The overall yield of 2-phenylpyrrocoline was 51%.

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