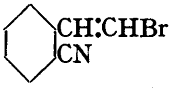
80. *A New General Synthesis of* 1-iso*Quinoline Derivatives.*

By W. DAVIES, J. F. KEFFORD, and J. L. OSBORNE.

The Grignard reagent R•MgX (where R is methyl, phenyl, or benzyl) reacts additively with the cyano-group in *trans*-ω-bromo-*o*-cyanostyrene; when the product is heated from 100° to 200°, MgXBr is eliminated, and the 1-substituted *iso*quinoline produced. The yield is small owing to the formation of by-products, but the *iso*quinoline derivative is readily obtained pure.

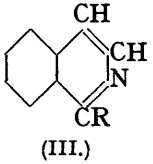
*iso*QUINOLINE derivatives substituted in the 1-position are important from the point of view of alkaloidal chemistry. The reduced *iso*quinolines of this type have long been known (Bischler and Napieralski, *Ber.*, 1893, **26**, 1903; Pictet and Kay, *Ber.*, 1909, **42**, 1973; Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 299), but their conversion into *iso*quinolines proved a stumbling block until Späth and Burger (*Ber.*, 1927, **60**, 704) and especially Späth, Berger, and Kuntara (*Ber.*, 1930, **63**, 134) showed that dehydrogenation was effected by heating with " palladium mohr " at 190—200°. This method suffers from the necessity of the tedious separation of the very soluble homamine and the dihydro*iso*quinoline derived from it. In the present work the direct synthesis is effected without recourse to any hydrogenated type.

trans-ω-Bromo-*o*-cyanostyrene (I) (preceding paper) in ether is added to a Grignard reagent RMgX (preferably two molecules). When the preliminary reaction is complete, the ether is removed by distillation, and the residue heated from 100° to 200°; the intermediate compound (II) then loses magnesium halogenobromide, and the 1-substituted *iso*quinoline (III) formed. The product is acidified, and any unchanged (I), ketone or hydrocarbon removed in steam; treatment with alkali, followed by steam distillation, then gives the desired base pure apart from moisture. In this way 1-methyl-, 1-phenyl-, and 1-benzyl-*iso*quinolines have been prepared from methyl iodide, bromobenzene, and benzyl bromide respectively. The yield does not exceed 15½%, owing partly to incomplete decomposition of the addition compound (II), but chiefly to the formation of a non-volatile product, which is being investigated.

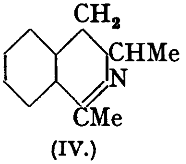


(I.)

(II.)



(III.)



(IV.)

The homogeneity of 1-methyl*iso*quinoline thus produced has been particularly investigated, as this base was synthesised by one of us in 1926 (from *cis*-ω-bromo-*o*-cyanostyrene, m. p. 30°) and not recognised because the melting points ascribed up to 1930 to some of the crystalline derivatives of 1-methyl*iso*quinoline are incorrect; *e.g.*, the highest recorded melting point of the picrate is 16° low. The identity of the base synthesised as described above has been proved by the method of mixed melting points, its picrate (m. p. 225—226°) and that of authentic 1-methyl*iso*quinoline (Späth, Berger, and Kuntara, *loc. cit.*) being used.

Consideration of the possible formation of a mixture of bases by the above synthesis is necessary because it has been claimed (for references, see Courtot, " Magnesium en Chimie Organique," 1926, p. 316) that Grignard reagents add on to ethylenic linkages. Had MeMgI added partly on to the double bond as well as on the the CN group in (I), the 1-methyl*iso*quinoline would have been contaminated with 1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline (IV) (picrate, m. p. 136°; Hey, J., 1930, 18) or with 1 : 4-dimethyl-3 : 4-dihydro*iso*quinoline (picrate, m. p. 167—168°; Späth, Berger, and Kuntara, *loc. cit.*). The absence from the synthetic product of these or comparable bases shows that the ethylene bond in (I) does not add on a Grignard reagent. This inertia of a single ethylenic bond is in accord with the non-addition of phenylmagnesium bromide to styrene at 130—160° (Kinney and Larsen, *J. Amer. Chem. Soc.*, 1935, **57**, 1054). These instances, together with the exhaustive investigation at lower temperatures of more than thirty unsaturated hydrocarbons by Gilman and collaborators (see Gilman and Schulz, *ibid.*, 1930, **52**, 3588, for references), show that the possibility of this type of addition is unlikely to cause serious ambiguity in synthetic work.

EXPERIMENTAL.

1-*Methyl*iso*quinoline.*—A solution of *trans*-ω-bromo-*o*-cyanostyrene (4·5 g.; 1 mol.) in dry ether was added to the Grignard compound (2 mols.) prepared from 6·2 g. of methyl iodide and 1·06 g. of magnesium; a white precipitate at once formed. The mixture was refluxed for 15 minutes, the ether distilled off, and the residue heated on a water-bath for 1 hour and in it for 15 minutes. The product was acidified with dilute sulphuric acid and subjected to steam-distillation; from the distillate, ether extracted a small quantity of a fragrant oil, ω-bromo-*o*-acetylstyrene, of which the 2 : 4-*dinitrophenylhydrazone* formed red crystals, m. p. 182°, from ethyl alcohol or acetone (Found: N, 13·7. $C_{16}H_{13}O_4N_4Br$ requires N, 13·8%). The acid residue was made alkaline with sodium hydroxide solution. Steam-distillation removed a reddish oil with a pleasant basic smell (0·4 g.; 13% yield), which was isolated by means of ether. The methiodide crystallised from alcohol in needles, m. p. 204—205° (1-methyl*iso*quinoline methiodide has m. p. 207·5°; Mills and Smith, J., 1922, **121**, 2732); the picrate, prepared in alcoholic solution, crystallised from methyl alcohol in yellow needles (Found: N, 15·2. Calc. for $C_{10}H_9N,C_6H_3O_7N_3$: N, 15·1%), m. p. 225—226° alone or mixed with authentic 1-methyl*iso*quinoline picrate, m. p. 225—226° (Späth, Berger, and Kuntara, *loc. cit.*).

1-*Phenyl*iso*quinoline.*—Similarly, from bromobenzene (7·6 g.; 2 mols.), magnesium (1·17 g.; 2 mols.), and *trans*-ω-bromo-*o*-cyanostyrene (5 g.; 1 mol.), 0·61 g. (12·5% yield) of 1-phenyl*iso*quinoline was obtained. After removal of the ether the residue was heated for an hour in an oil-bath at 160° [a better yield (0·79 g.; 15·5%) of the base was later obtained by 2½ hours' heating at 200°]. The base, filtered from the final steam-distillate and crystallised from light petroleum, had m. p. 95—96°; its picrate (from ethyl alcohol) had m. p. 165—166°. These are the m. p.'s recorded by Späth, Berger, and Kuntara (*loc. cit.*) for 1-phenyl*iso*quinoline and its picrate. The preliminary steam-distillation of the acidified reaction product gave some unchanged *trans*-ω-bromo-*o*-cyanostyrene, diphenyl (m. p. 69°), and a small quantity of a fragrant oil, ω-bromo-*o*-benzoylstyrene, of which the 2 : 4-*dinitrophenylhydrazone* formed orange crystals, m. p. 206—207°, from dioxan (Found: N, 12·3. $C_{21}H_{15}O_4N_4Br$ requires N, 12·0%).

1-*Benzyl*iso*quinoline.*—This was similarly obtained (0·2 g.; 4% yield) from benzyl bromide (8·2 g.; 2 mols.), magnesium (1·17 g.; 2 mols.), and *trans*-ω-bromo-*o*-cyanostyrene (5 g.; 1 mol.); the temperature of the product was gradually raised to 170° and maintained for an hour. The base formed a picrate having the m. p., 182°, recorded by Späth, Berger, and Kuntara (*loc. cit.*). The amount of by-product non-volatile in steam was unusually large (4·2 g.). Steam-distillation of the acidified reaction product gave dibenzyl (0·45 g.; m. p. 52·5°) and a fragrant oil, ω-bromo-*o*-phenylacetylstyrene, of which the brick-red 2 : 4-*dinitrophenylhydrazone* formed crystals, m. p. 162·5°, from dioxan (Found: N, 11·9. $C_{22}H_{17}O_4N_4Br$ requires N, 11·7%).

THE UNIVERSITY OF MELBOURNE.

[*Received, November 17th,* 1938.]