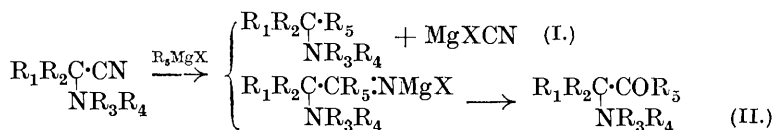


CCCLVIII.—*Action of the Grignard Reagent upon Amino-nitriles.*

By THOMAS STEVENS STEVENS, JOHN MURDOCH COWAN, and JOHN MACKINNON.

INCIDENTALLY to another investigation (Stevens, J., 1930, 2109) the action of phenylmagnesium bromide on α -dimethylamino- β -phenylpropionitrile, $\text{CH}_2\text{Ph}\cdot\text{CH}(\text{NMe}_2)\cdot\text{CN}$, was studied: the expected ketone, $\text{CH}_2\text{Ph}\cdot\text{CH}(\text{NMe}_2)\cdot\text{COPh}$, was not obtained, but instead the cyano-group was replaced by phenyl, yielding $\text{CH}_2\text{Ph}\cdot\text{CH}(\text{NMe}_2)\text{Ph}$. This process has now been applied to other amino-nitriles, and it has been found that the reaction may either take the course of double decomposition as above (I), or, less frequently, the normal one of ketone formation (II).



The greater part of this investigation was carried out in ignorance of the work of Bruylants and his collaborators (*Bull. Acad. roy. Belg.*, 1924, **10**, 166 and subsequent papers), who have found that the reaction (I) occurs with a large number of tertiary α -amino-nitriles; piperidino-nitriles were principally studied.*

The results, summarised in the table below, are of a preliminary

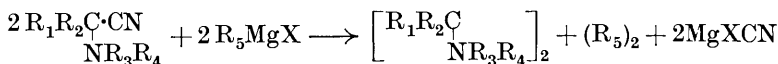
* We have been in communication with Professor Bruylants, who has kindly expressed his willingness that we should pursue this investigation.

nature, and it is not claimed that in every case the reaction has proceeded exclusively in the direction stated.

R ₁ R ₂ .	R ₃ R ₄ .	R ₅ .	Product.	R ₁ R ₂ .	R ₃ R ₄ .	R ₅ .	Product.
H, H	Me, Me	Me	I and II	H, Ph	Me, Me	Me	I
H, H	Me, Me	Ph	II	H, Ph	Me, Me	Ph	I
H, H	H, Ph	Me	I	H, Ph	Me, Me	CH ₂ Ph	I
H, H	Et, Ph	Me	II	H, CH ₂ Ph	Me, Me	Ph	I
H, Me	C ₅ H ₁₀ >	Ph	I				

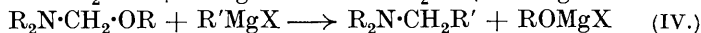
Nitriles containing the group NH₂ or NHMe, of which methyl-aminoacetonitrile was examined with considerable thoroughness, did not give favourable results; Bruylants records similar observations.

The "normal" Grignard-nitrile reaction (II) was only observed in cases for which R₁ = R₂ = H; it was not encountered by the Belgian investigators, who studied only one compound of the type indicated. On the other hand, the reaction

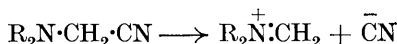


which they frequently observed, especially when both R₁ and R₂ were hydrocarbon radicals, has not been met with in the present study.

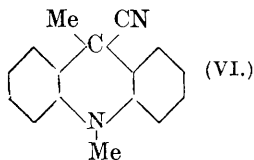
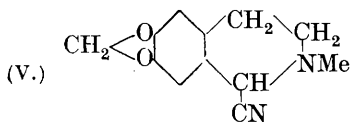
The reaction (I), and also the processes (III) (Späth, *Monatsh.*, 1914, **35**, 319) and (IV) (Robinson and Robinson, *J.*, 1923, **123**, 532),



and others, can be correlated (empirically or otherwise) with the formal structural possibility of ionisation of the type



Then mobility of the cyano-group would be associated with that structural environment which confers "pseudo-basic" properties on a hydroxyl radical. Accordingly the nitriles (V) and (VI) (a γ -amino-nitrile), corresponding to notoriously "pseudo-basic" alcohols, were investigated; as anticipated, they reacted with methylmagnesium iodide according to scheme (I).



The association of the reaction course (II), in place of (I), with the group $>\text{N} \cdot \text{CH}_2 \cdot \text{CN}$ may be classified along with the fact that in

reaction (III) formals are attacked by the Grignard reagent much less readily than the higher acetals. In each case the presence of hydrocarbon substituents in the methylene group favours the process of double decomposition.

EXPERIMENTAL.

The known amino-nitriles were prepared in each case according to the authority cited; in reactions of the Strecker type, it was often found convenient to employ the combination: aldehyde-potassium cyanide-amine hydrochloride or amine + acetic acid, the use of hydrogen cyanide or the conversion of the aldehyde into bisulphite compound being avoided.

The amino-nitrile (1 mol.), diluted with ether, was added gradually to the cooled Grignard reagent (2 mols.), and, after 15 hours, the whole was warmed on the water-bath. Unless otherwise stated, the mixture was treated with ice and sulphuric acid, and the acid layer separated, basified, and distilled in steam. The acid in salts of tertiary bases was estimated by titration with alcoholic potash, with phenolphthalein as indicator.

Dimethylaminoacetonitrile (von Braun, *Ber.*, 1907, **40**, 3937).—In the reaction with methylmagnesium iodide, the volatile bases were collected in hydrochloric acid. The solution was evaporated to dryness and the bases were liberated by concentrated aqueous alkali in presence of ether. On distillation of the dried ethereal solution (column), ethyldimethylamine passed over with the ether; it was converted into the picrate, m. p. 200° (Hanhart and Ingold, *J.*, 1927, 1006, give m. p. 200—201°) (Found: $C_6H_3O_7N_3$, 74.6. Calc. for $C_4H_{11}N, C_6H_3O_7N_3$: $C_6H_3O_7N_3$, 75.6%). After removal of the ether, the residue distilled at 123°, and yielded a methiodide, m. p. 167° alone or mixed with authentic acetyltrimethylammonium iodide (Stoermer and Dzinski, *Ber.*, 1895, **28**, 2223).

The same amino-nitrile, treated with phenylmagnesium bromide, gave phenacyldimethylamine, which was isolated as the picrate, m. p. 141°, identical with a specimen prepared from authentic phenacyldimethylamine (benzyldimethylamine picrate melts at 94°).

Anilinoacetonitrile (Bucherer and Schwalbe, *Ber.*, 1906, **39**, 2800) with methylmagnesium iodide yielded ethylaniline, b. p. 206°, m. p. and mixed m. p. of hydrochloride, 176—178°.

Ethylanilinoacetonitrile.—The preparation described by Knoevenagel (*Ber.*, 1904, **37**, 4083) gave unsatisfactory results, and attempted modifications led to little improvement. The nitrile was converted by methylmagnesium iodide into ethylanilinoacetone, b. p. 143°/11 mm. This product, which does not appear to have been described, was characterised as the *phenylhydrazone*, colourless

leaflets from methyl alcohol, m. p. 96° (Found : N, 15.5. $C_{17}H_{21}N_3$ requires N, 15.7%); this derivative decomposed spontaneously, under conditions which have not been defined. For comparison, the ketone was synthesised by warming a mixture of ethylaniline (2 mols.) and bromoacetone (1 mol.) to 30° . Reaction set in with evolution of much heat, and, after addition of benzene, the solution was filtered from ethylaniline hydrobromide and distilled in a vacuum. The ketone obtained yielded a phenylhydrazone identical with that just described.

α -Piperidinopropionitrile (Knoevenagel, *loc. cit.*, p. 4086) yielded with phenylmagnesium bromide 1- α -phenylethylpiperidine, a colourless, unpleasant-smelling oil, volatile in steam. The *picrate*, conveniently prepared in ether, crystallised from alcohol in irregular, deep yellow prisms, m. p. 140 — 142° (Found : $C_6H_5O_7N_3$, 54.5. $C_{13}H_{19}N,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 54.8%). For comparison, the same substance was prepared as follows (reaction of Leuckart and Wallach) : acetophenone (1 mol.), piperidine (1 mol.), and formic acid (80% ; 2—3 mols.) were heated at 170 — 200° for 3 hours (sealed tube). The basified product was extracted with benzene, and the benzene layer thoroughly washed with water and evaporated. The residue, on treatment with ethereal picric acid solution, gave α -phenylethylpiperidine *picrate*, identical with that described above.

α -Dimethylaminophenylacetoneitrile, prepared from benzaldehyde, dimethylamine, potassium cyanide, and acetic acid in cold aqueous alcohol, boiled at $120^{\circ}/16$ mm. (equiv., by decomposition with acid and back-titration with alkali and methyl-red, 159. $C_{10}H_{12}N_2$ requires equiv., 160). With methylmagnesium iodide it gave α -phenylethyldimethylamine, isolated as the *picrate*, m. p. and mixed m. p. 137 — 139° (compare Stevens, *loc. cit.*). Treatment with phenylmagnesium bromide yielded benzhydryldimethylamine, m. p. and mixed m. p. 68 — 69° (Stevens, *loc. cit.*). By the action of benzylmagnesium chloride, $\alpha\beta$ -diphenylethyldimethylamine was produced as an oil, which distilled slowly in steam, and gave a *hydrochloride* crystallising from alcohol-ether in colourless needles or stout laminae, m. p. 187 — 188° (Found : HCl, 13.9. $C_{16}H_{19}N,HCl$ requires HCl, 14.0%). Dry distillation of the hydrochloride yielded stilbene, m. p. and mixed m. p. 122 — 124° . The *picrate* crystallised from methyl alcohol in yellow leaflets, which, even after frequent recrystallisation, softened markedly at 130° and melted at 156 — 157° (Found : $C_6H_3O_7N_3$, 50.4. $C_{16}H_{19}N,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 50.4%).

Synthesis of $\alpha\beta$ -Diphenylethyldimethylamine.—Deoxybenzoinoxime was reduced in boiling alcohol with a moderate excess of sodium amalgam, the solution being kept faintly acid with acetic acid. The

product was diluted with water, extracted with benzene, basified, and again extracted. From the second extract, gaseous hydrogen chloride precipitated $\alpha\beta$ -diphenylethylamine hydrochloride, m. p. 253°. Konowalow (*Ber.*, 1895, **28**, 1860) gives 251.5—252.5°; other workers record lower values. The acetyl and benzoyl derivatives melted at 148° and 177° respectively, as found by Leuckart and Janssen (*Ber.*, 1889, **22**, 1412). The hydrochloride was methylated by heating with excess of formalin (38%) at 130° for 3 hours. After a considerable quantity of neutral material had been removed by extraction, the liquors were basified, and the base was extracted and converted into the hydrochloride, identical with the above.

α -Dimethylamino- β -phenylpropionitrile was obtained as an oil, b. p. 148—150°/25 mm., when phenylacetaldehyde sodium bisulphite was left over-night with a slight excess of potassium cyanide and dimethylamine in aqueous solution. The *hydrochloride* crystallised from alcohol-ether in colourless needles, m. p. ca. 170° (efferv.) (Found: Cl, 16.7. $C_{11}H_{14}N_2 \cdot HCl$ requires Cl, 16.8%). Treatment with phenylmagnesium bromide gave $\alpha\beta$ -diphenylethylamine, identified as hydrochloride and picrate.

1-Cyanohydrohydrastinine (V) (Dobbie and Tinkler, *J.*, 1904, **85**, 1009).—After reaction with methylmagnesium iodide, the mixture was treated with ice and ammonium chloride, and the ethereal layer washed thoroughly with water and extracted with dilute hydrochloric acid. Addition of solid potassium iodide to the acid extract precipitated 1-methylhydrohydrastinine as hydriodide, identical, m. p. and mixed m. p., with a specimen prepared from hydrastinine hydrochloride and methylmagnesium iodide, as described by Freund and Lederer (*Ber.*, 1911, **44**, 2357). The methiodide melted at 230°, as found by Freund and Lederer.

9-Cyano-9 : 10-dimethyl-9 : 10-dihydroacridine (VI) was prepared according to Kaufmann and Albertini (*Ber.*, 1911, **44**, 2055), but methylacridine methosulphate was used in place of the methochloride. The reaction product was decomposed with ice and ammonium chloride, and the washed and dried ethereal solution gave on evaporation 9 : 9 : 10-*trimethyl*-9 : 10-*dihydroacridine* (Found: C, 85.5; H, 7.5. $C_{16}H_{17}N$ requires C, 86.1; H, 7.6%). The action of methylmagnesium iodide on methylacridine methiodide yielded an identical product, isolated in a similar manner (compare Freund and Bode, *Ber.*, 1909, **42**, 1755).

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