387. *Action of the Grignard Reagent upon Amino-nitriles. Part II.*

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An α-aminonitrile and a Grignard reagent may interact in either of three ways (Bruylants, *Bull. Acad. roy. Belg.*, 1924, **10**, 166; 1925, **11**, 261; Stevens, Cowan, and MacKinnon, J., 1931, 2568, regarded as Part I of this series); thus R″MgX and R·CH(NR′$_2$)·CN may give

$$\mathrm{R{\cdot}CH(NR'_2){\cdot}R''}\ \text{(I)},\quad \mathrm{R{\cdot}CH(NR'_2){\cdot}COR''}\ \text{(II)},$$

or

$$\mathrm{R{\cdot}CH(NR'_2){\cdot}CH(NR'_2){\cdot}R}\ \text{(III)}.$$

The present study is principally concerned with the effect upon the reaction course of altering R and R″ while R′ = Me; most of the cases recorded in Part I have been re-examined. Reaction (III) has not been encountered with dimethylamino-nitriles.

The results, collected in Table I, lead to the following rules: (*a*) When R = H, (II) predominates, irrespective of the nature of R″. (*b*) When R is a lower alkyl, (II) predominates if R″ is alkyl, and (I) if R″ is Ph or CH_2Ph. (*c*) When R = Ph, the main product is always (I).

Rule (*a*) was commented upon in Part I. The controlling factor in the cases falling under (*b*) is not simply the *weight* of R, since *cyclo*hexyl behaves like the simple alkyls [case B(4) in Table I].

It is consistent with general experience that double decomposition (reaction I) is strongly favoured by insertion of Ph in the α-position to the replaceable (CN) group (rule *c*), but the similar effect of β-phenylation [case F(2)] was not anticipated.

The sensitiveness of the reaction to small constitutional changes is well shown by the effect of replacing the dimethylamino- by the piperidino-group in the nitrile; the results in Table I show complete suppression of reaction (II). As Bruylants's result for H(1) was especially surprising, the experiment has been repeated and confirmed. The exclusive formation of product (I) is apparently not due to some specific property of the heterocyclic piperidino-radical, for Bruylants (*loc. cit.*) obtained 83% of product (I) from α-dimethylamino-*n*-valeronitrile and ethylmagnesium bromide. The considerations advanced in Part I suggest that these differences may be associated with the basic strength of the amino-nitrogen atom, amino-nitriles derived from piperidine or diethylamine undergoing reaction (I) more readily than those derived from the weaker bases dimethylamine and ethylaniline (compare Part I), but the matter requires further investigation.

TABLE I.

[The numbers recorded are percentage yields of products of types (I) and (II); *m* signifies main product.]

Dimethylamino-nitriles ($NR'_2 = NMe_2$).

R in R·CH(NR′₂)·CN.	Grignard Reagent. (1) MeMgI. (I)	(II)	(2) EtMgBr. (I)	(II)	(3) $Pr^{\alpha}MgBr$. (I)	(II)	(4) $C_6H_{11}MgCl$. (I)	(II)
(A) H	4	50 [2]	0	60	0	58	—	
(B) Me	14	50	13	50	0	67	0	64
(C) Pr^{α}	0	53	—		—		—	
(D) $CH_2(NMe_2)\cdot CH_3$	—		—		—		—	
(E) CHMe:CH	—		—		—		—	
(F) CH_2Ph	—		89	0 [3]	—		—	
(G) Ph	71	0 [2]	—		89	0 [3]	—	

R in R·CH(NR′₂)·CN.	Grignard Reagent. (5) CH:CMgBr. (I)	(II)	(6) $CH_2Ph\cdot MgCl$. (I)	(II)	(7) PhMgBr. (I)	(II)
(A) H	no reacn.		0	>50	0	78 [2]
(B) Me	—		76	0	78	0
(C) Pr^{α}	—		—		71	0 [3]
(D) $CH_2(NMe_2)\cdot CH_2$	—		67	0 [3]	*m*	0 [4]
(E) CHMe:CH	—		—		60	0 [4]
(F) CH_2Ph	—		—		*m*	— [1]
(G) Ph	—		*m*	— [1]	63	0 [2]

Piperidino-nitriles ($NR'_2 = C_5H_{10}N$).

	Grignard Reagent. (1) MeMgI. (I)	(II)	(2) EtMgBr. (I)	(II)	(6) $CH_2Ph\cdot MgCl$. (I)	(II)	(7) PhMgBr. (I)	(II)
(H) H	50	0 [4*]	—		—		—	
(J) Me	*m*	0 [4*]	—		63	0 [6]	63	0 [2]
(K) Et	*m* †	0 [4*]	—		90	0 [4]	*m*	0 [4]
(L) CH_2:CH	—		—		—		40	0 [4]
(M) Ph	—		80	0 [5]	60	0 [5*]	83	0 [5]

[1] Part I (*loc. cit.*). [2] Re-examination of case studied in Part I. [3] Compare Thomson and Stevens (this vol., p. 1932); EtMgI was used in case F(2). [4] Bruylants (*locc. cit.*). [5] Christiaen (*Bull. Soc. chim. Belg.*, 1924, **33**, 483). [6] Derived from "competitive" experiment (compare p. 2611). * Grignard reagent of type RMg*Br*. † Almost quantitative.

The interpretation of the results of this study is difficult, because the effect of a given structural change upon the nature of the final product may be regarded as compounded of its separate effects upon the velocities of the individual reactions (I) and (II). In order to obtain some indication of the nature of these effects in cases B(1), B(6), and B(7) (dimethylamino-propionitrile and different Grignard reagents), the Grignard reagents were allowed to compete in pairs (1 mol. of each) for 1 mol. of (*a*) propionitrile [reaction exclusively

according to (II)] and (*b*) piperidinopropionitrile [reaction solely according to (I)]. The results are expressed as percentage yields of product, calculated on the nitrile used :

	MeMgI : $CH_2Ph{\cdot}MgCl$.		MeMgI : PhMgBr.	
$Me{\cdot}CH_2{\cdot}CN$	23	38	0	67
$Me{\cdot}CH(NC_5H_{10}){\cdot}CN$	0	63	0	60

They are consistent with those in Table I. They show (the method being assumed valid) that *both* reactions can be strongly affected, and in the same sense, by the same constitutional change; and, in particular, that the exclusive appearance of product (I) in cases B(6) and B(7) is not due to inhibition of reaction (II).

EXPERIMENTAL.

The amino-nitriles were prepared as described in Part I, the known substances having the properties ascribed to them in the literature. The amino-nitrile (1 mol.) in Et_2O was gradually added to the cooled Grignard reagent (2 mols.) and, after 15 hrs., the products were obtained in Et_2O, *either* after decomp. with ice and NH_4Cl, *or* after treatment with dil. H_2SO_4 and steam-distillation of the basified acid layer into dil. HCl, followed by evaporation of the HCl and basification of the residue with conc. NaOH in presence of Et_2O. The method used in each individual case is specified respectively by " NH_4Cl " or " H_2SO_4," and the word " negative " refers to the result of the qualitative test (below) for product (I).

Preliminary expts. on the quant. separation of products of types (I) and (II) were carried out with mixtures of $CH_2Ph{\cdot}NMe_2$ and $Ph{\cdot}CO{\cdot}CH_2{\cdot}NMe_2$. Methods depending on the use of reagents for the CO group, or on the difference in basic strength between the two products, were not satisfactory. After reduction of the mixed methosulphates by Zn–AcOH, (I) was recovered quantitatively as methopicrate, and (II) in part as COPhMe. This process was used to identify many of the ketonic bases as N-free ketones (included below, without further comment, among the derivatives of the amino-ketones), and also as a qual. test for product (I); the test is regarded as reliable and sensitive, except possibly for the bases of lowest mol. wt.

As these methods were not quant., the products were separated as far as possible by distillation [in cases A(1), B(1), and B(2), some or all of product (I) distilled with the Et_2O], and the fractions were converted into cryst. derivatives, usually picrates, whose homogeneity was carefully examined. The materials were so tractable that the zero values in Table I are considered to represent at most very small quantities of the corresponding substances, especially of products (I). The same applies to the figures quoted from Bruylants and from Christiaen, who used relatively large quantities of materials, and state expressly that formation of (II) was never observed.

(A) Dimethylaminoacetonitrile (von Braun, *Ber.*, 1907, **40**, 3937); *picrate*, fine, yellow needles, m. p. 168—169°, from EtOH (Found : $C_6H_3O_7N_3$, 73·4. $C_4H_8N_2$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 73·2%).

(2) EtMgBr (H_2SO_4; negative) gave dimethylaminomethyl ethyl ketone; hydrochloride and hydrobromide non-cryst.; picrate difficult to purify; p-*bromophenacylobromide*, small prisms, m. p. 180—181° (decomp.), from EtOH–Et_2O (Found : ionisable Br, 20·1. $C_{14}H_{19}O_2NBr{\cdot}Br$ requires ionisable

Br, 20·4%); methyl ethyl ketone 2 : 4-dinitrophenylhydrazone, fine, orange-red needles, m. p. and mixed m. p. 111—112°, from EtOH (Found: N, 22·3. Calc. for $C_{10}H_{12}O_4N_4$: N, 22·2%).

(3) Pr$^{\alpha}$MgBr (H_2SO_4; negative) gave dimethylaminomethyl *n*-propyl ketone; p-*bromophenacylobromide*, minute prismatic needles, m. p. 178—181° (decomp.; softening at 175°), from EtOH–Et_2O (Found: ionisable Br, 19·4. $C_{15}H_{21}O_2NBr{\cdot}Br$ requires ionisable Br, 19·7%); *methyl* n-*propyl ketone* 2 : 4-*dinitrophenylhydrazone*, orange-red leaflets, m. p. and mixed m. p. 142—143°, from EtOH (Found: N, 21·0. $C_{11}H_{14}O_4N_4$ requires N, 21·1%).

(5) The amino-nitrile after treatment with CH:C·MgBr (Salkind and Rosenfeld, *Ber.*, 1924, **57**, 1690) was recovered quantitatively as picrate. No attempt was made to "force" the reaction by heating.

(6) The crude product (yield 75%) of the reaction with $CH_2Ph{\cdot}MgCl$ (H_2SO_4; negative) decomposed partially on steam-distillation. *Dimethylaminomethyl benzyl ketone hydrobromide* formed fine needles or minute, short prisms, m. p. 151—153°, from EtOH–Et_2O (Found: HBr, 31·9. $C_{11}H_{15}ON$,HBr requires HBr, 31·4%); phenylacetone semicarbazone, m. p. 187—189° (Wolff, *Annalen*, 1902, **325**, 146, gives m. p. 188—189°), and phenylhydrazone, m. p. 83—85° (Miller and Rohde, *Ber.*, 1890, **23**, 1074, give m. p. 85°).

(7) PhMgBr (NH_4Cl; negative) gave phenacyldimethylamine; picrate, m. p. and mixed m. p. 143°; acetophenone phenylhydrazone, m. p. and mixed m. p. 105—106°.

(B) α-Dimethylaminopropionitrile (Henry, *Bull. Acad. roy. Belg.*, 1904, 741).

(1) MeMgI (H_2SO_4) gave dimethyl*iso*propylamine; *picrate*, fine, yellow needles, m. p. 240—241° (decomp.), from EtOH (Found: $C_6H_3O_7N_3$, 72·6. $C_5H_{13}N$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 72·5%): and also methyl α-dimethylaminoethyl ketone; *picrate*, m. p. 166—168° (after frequent recrystn. from EtOH to remove traces of dimethyl*iso*propylamine picrate) (Found: $C_6H_3O_7N_3$, 66·9. $C_6H_{13}ON$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 66·6%); methyl ethyl ketone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 111—112°. For comparison, dimethyl*iso*propylamine was prepared by Eschweiler methylation of *iso*propylamine (Goldschmidt, *Ber.*, 1887, **20**, 728); the diluted reaction product was evap. to dryness and the base, liberated by conc. NaOH in presence of Et_2O, converted into picrate, identical with that described above.

(2) EtMgBr (H_2SO_4) gave dimethyl-*sec.*-butylamine; *picrate*, fine, yellow needles, m. p. 192—193°, from EtOH (Found: $C_6H_3O_7N_3$, 69·6. $C_6H_{15}N$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 69·4%): and also ethyl α-dimethylaminoethyl ketone; *picrate*, minute yellow prisms, m. p. 161—163°, from acetone (Found: $C_6H_3O_7N_3$, 64·5. $C_7H_{15}ON$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 64·0%); diethyl ketone semicarbazone, m. p. 138—139° (Dilthey, *Ber.*, 1901, **34**, 2122, gives m. p. 139°). For comparison, dimethyl-*sec.*-butylamine, picrate identical with that just described, was prepared by Eschweiler methylation of *sec.*-butylamine (Freylon, *Ann. Chim.*, 1908, **15**, 285).

(3) Pr$^{\alpha}$MgBr (H_2SO_4; negative) gave α-dimethylaminoethyl *n*-propyl ketone; *picrate*, small yellow prisms, m. p. 200—201°, from acetone (Found: $C_6H_3O_7N_3$, 62·0. $C_8H_{17}ON$,$C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 61·6%); ethyl propyl ketone semicarbazone, m. p. 110°, as found by Blaise (*Compt. rend.*, 1901, **133**, 1218). *β-Dimethylaminopentane picrate*, synthesised for comparison in the same way as dimethyl*iso*propylamine picrate, formed small, yellow prisms from acetone, m. p. 208—210°, strongly depressed on admixture

with dimethylaminoethyl *n*-propyl ketone picrate (Found: $C_6H_3O_7N_3$, 66·4. $C_7H_{17}N,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 66·6%).

(4) *cyclo*Hexylmagnesium chloride (NH_4Cl) gave *cyclo*hexyl α-dimethylaminoethyl ketone, b. p. 220—240°; *picrate*, difficultly crystallisable, yellow prisms, m. p. 165—167°, from MeOH (Found: $C_6H_3O_7N_3$, 55·9. $C_{11}H_{21}ON,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 55·6%); p-*bromophenacylobromide*, minute, prismatic needles, m. p. 213—214° (decomp.), from EtOH–Et_2O (Found: ionisable Br, 17·2. $C_{19}H_{27}O_2NBr{\cdot}Br$ requires ionisable Br, 17·4%); *cyclo*hexyl ethyl ketone semicarbazone, m. p. 149—150°, as found by Hell and Schaal (*Ber.*, 1909, **42**, 2232).

(6) $CH_2Ph{\cdot}MgCl$ (NH_4Cl) gave β-dimethylamino-α-phenylpropane, pale yellow liquid, b. p. 148—150°/100 mm.; methiodide, rectangular prisms, m. p. 227—228° (von Braun, Heider, and Neumann, *Ber.*, 1916, **49**, 2618, give m. p. 228°), from EtOH (Found: I, 41·4. Calc. for $C_{12}H_{20}NI$: I, 41·6%); *methopicrate*, yellow prisms, m. p. 103—105°, from EtOH–H_2O (Found: $C_6H_2O_7N_3'$, 56·4. $C_{12}H_{20}N{\cdot}C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 56·2%).

(7) PhMgBr (NH_4Cl) gave α-phenylethyldimethylamine, b. p. 194—195°; picrate, yellow leaflets, m. p. and mixed m. p. 136—139°, from MeOH–H_2O (Stevens, J., 1930, 2113).

(C) α-Dimethylamino-*n*-valeronitrile boiled at 170—175° (Henry, *Bull. Acad. roy. Belg.*, 1898, **36**, 245, gives b. p. 175—176°).

(1) MeMgI (H_2SO_4; negative) gave methyl α-dimethylamino-*n*-butyl ketone; *picrate*, stout, yellow, prismatic needles, m. p. 118—120°, from EtOH (Found: $C_6H_3O_7N_3$, 61·9. $C_8H_{17}ON,C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 61·6%); methyl *n*-butyl ketone semicarbazone, m. p. 126—127° (Bouveault and Locquin, *Bull. Soc. chim.*, 1904, **31**, 1157, give m. p. 127°).

(H) Piperidinoacetonitrile (Knoevenagel, *Ber.*, 1904, **37**, 4082).

(1) MeMgI (H_2SO_4) yielded ethylpiperidine (50%), b. p. 126—129°; picrate, fern-like aggregates of yellow prisms, m. p. 167—168°, from EtOH (Found: $C_6H_3O_7N_3$, 67·2. Calc. for $C_7H_{15}N,C_6H_3O_7N_3$: $C_6H_3O_7N_3$, 67·0%). Bruylants (*loc. cit.*) gives base, b. p. 128—129°; picrate, m. p. 165°. A small amount of a higher-boiling liquid was also obtained, as found by Bruylants, which gave an apparently homogeneous methiodide, prismatic needles, m. p. 296—297° (decomp.), from EtOH–Et_2O; acetonylpiperidine methiodide melts at 126° (Stormer and Burkert, *Ber.*, 1895, **28**, 1251).

Competitive Experiments.—The nitrile (1 mol.) was added to the Grignard reagents (1 mol. of each, estimated by acid titration; compare Gilman and Meyer, *Rec. trav. chim.*, 1926, **45**, 314) in Et_2O.

Propionitrile (Walden, *Ber.*, 1907, **40**, 3216) gave with MeMgI + $CH_2Ph{\cdot}MgCl$ (H_2SO_4), methyl ethyl ketone (weighed as 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 111—112°) and also benzyl ethyl ketone (b. p. 222—227°; semicarbazone, m. p. 150—153°: Tiffeneau and Fourneau, *Compt. rend.*, 1908, **146**, 699, give m. p. 153°); 2 : 4-*dinitrophenylhydrazone*, fine, deep-yellow needles, m. p. 140—141°, from EtOH (Found: N, 17·2. $C_{16}H_{16}O_4N_4$ requires N, 17·1%). MeMgI + PhMgBr (H_2SO_4) gave only propiophenone, b. p. 217—220°; 2 : 4-*dinitrophenylhydrazone*, red leaflets, m. p. and mixed m. p. 187—189°, from EtOH (Found: N, 17·8. $C_{15}H_{14}O_4N$ requires N, 17·8%).

α-Piperidinopropionitrile (Knoevenagel, *loc. cit.*) gave with MeMgI + $CH_2Ph{\cdot}MgCl$ (H_2SO_4) only α-phenyl-β-piperidinopropane; picrate, non-cryst.; p-*bromophenacylobromide*, minute prisms, m. p. 197—199°, from EtOH–

Et_2O (Found: ionisable Br, 16·8. $C_{22}H_{27}ONBr{\cdot}Br$ requires ionisable Br, 16·6%). For comparison, the same substance was prepared (reaction of Leuckart and Wallach) by heating benzyl ethyl ketone (1 mol.), piperidine (1 mol.), and formic acid (80%; 2—3 mols.) at 170—200° for 3 hrs. (sealed tube). The C_6H_6 extract of the basified product was thoroughly washed with H_2O, evaporated, and the residue converted into *p*-bromophenacylobromide, identical with that described above. With the same nitrile, MeMgI + PhMgBr (H_2SO_4) gave only 1-α-phenylethylpiperidine; picrate, m. p. and mixed m. p. 145—147° (softens at 142°) (cf. Stevens, Cowan, and MacKinnon, *loc. cit.*).

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