[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylations of α-Dimethylaminophenylacetonitrile with Alkyl Halides by Potassium Amide. Reactions of Products with Grignard Reagents[1]

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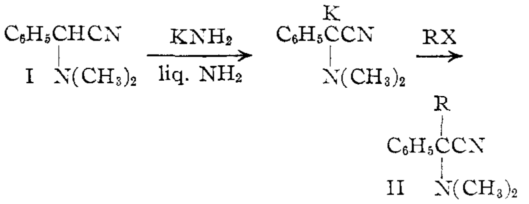
α-Dimethylaminophenylacetonitrile was methylated, ethylated, isopropylated and butylated with the appropriate halide by means of potassium amide in liquid ammonia. The resulting alkylation products were treated with acid to form the corresponding acylphenones and with Grignard reagents to produce two types of tertiary amines. One type of amine arose from the replacement of the cyanide group by the alkyl group of the Grignard reagent, and the other by replacement of the cyanide group by hydrogen. The latter reaction appears not to have been reported previously. Certain other reactions were observed.

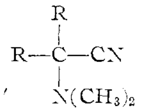
It has been shown[2] recently that α-dimethylaminophenylacetonitrile (I) can be alkylated with benzyl, benzhydryl and α-phenylethyl chlorides by means of sodium amide or potassium amide in liquid ammonia to form alkylation products of type II in which R is the corresponding benzyl type of group. The reaction may be represented by equation 1.



$$\underset{\text{I}}{C_6H_5\underset{N(CH_3)_2}{CH}CN} \xrightarrow[\text{liq. } NH_2]{KNH_2} C_6H_5\overset{K}{\underset{N(CH_3)_2}{C}}CN \xrightarrow{RX} \underset{\text{II}}{C_6H_5\overset{R}{\underset{N(CH_3)_2}{C}}CN} \qquad (1)$$

It has now been found that the α-aminonitrile I can be alkylated similarly with methyl iodide, and with ethyl, isopropyl and *n*-butyl bromides to form alkylation products of type II in which R is the corresponding purely aliphatic group (equation 1). In contrast to the earlier benzyl-type alkylation products, which underwent dehydrocyanation to form enamines on attempted distillation,[2] the present alkyl-type, alkylation products were distilled without noticeable decomposition. The yields and other data are summarized in Table I.

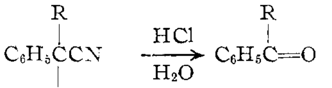
Since the α-aminonitrile I is readily prepared in excellent yield from benzaldehyde, dimethylamine and sodium cyanide, the alkylation according to equation 1 furnishes a convenient method of synthesis of α-aminonitriles of type II. In fact this appears to be the only reported preparation of these compounds, although the analogous α-aminonitriles II′ in which both of the R groups are aliphatic have been obtained from acetone, methyl ethyl ketone and other purely aliphatic ketones, secondary amines and an alkali cyanide.[3]



II′

$$R-\overset{R}{\underset{N(CH_3)_2}{C}}-CN$$

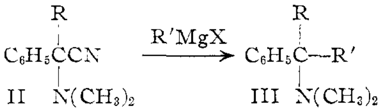
It can be seen from Table I that the yields of the alkylation products II were high (70–89%) not only with the primary halides but also with isopropyl bromide. However, the alkylation failed with *t*-butyl chloride under similar conditions. The α-aminonitrile structure for the alkylation products was indicated by analyses and by infrared spectra, which showed bands at about 2220 cm.$^{-1}$ for the nitrile groups. Their structures were established by acid-catalyzed hydrolysis to form the corresponding, known acylphenones in yields of 74–84% (equation 2).[4]



$$\underset{\text{II}}{C_6H_5\overset{R}{\underset{N(CH_3)_2}{C}}CN} \xrightarrow[H_2O]{HCl} C_6H_5\overset{R}{C}{=}O \qquad (2)$$

It was assumed previously that the analogous hydrolysis of the benzyl-type alkylation products II involved the intermediate formation of the corresponding enamines since not only were the α-aminonitriles readily dehydrocyanated to form the enamines but the latter compounds easily underwent hydrolysis to give the ketones. However, the present aliphatic alkylation products II appear not to produce enamines as intermediates, since they do not readily eliminate hydrogen cyanide. Instead the corresponding cyanohydrins might possibly be intermediates but this was not established.

Reactions of Alkylation Products II with Grignard Reagents.—It is well known that α-aminonitriles of types I and II′ generally react with Grignard reagents to form tertiary amines in which the cyanide group has been replaced by the alkyl or aryl group of the reagent. This course of reaction was observed also in the present work with some of the α-aminonitriles of type II and Grignard reagents to form tertiary amines of type III (equation 3).



$$\underset{\text{II}}{C_6H_5\overset{R}{\underset{N(CH_3)_2}{C}}CN} \xrightarrow{R'MgX} \underset{\text{III}}{C_6H_5\overset{R}{\underset{N(CH_3)_2}{C}}-R'} \qquad (3)$$

However, an apparently new course of reaction was realized with certain α-aminonitriles of type II and Grignard reagents, in which the cyanide group was replaced by hydrogen to form tertiary amines of type IV. This reaction, which evidently involves a hydride ion reduction to form an olefin as by-product, may be illustrated with isopropylmagnesium bromide (equation 4).

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[1] Supported by the National Science Foundation and by a Grant-in-aid from the Abbott Laboratories, North Chicago, Ill.

[2] C. R. Hauser, H. M. Taylor and T. G. Ledford, THIS JOURNAL, **82**, 1786 (1960).

[3] (a) P. Bruylants, *Bull. Acad. Roy. Belg.*, **11**, 261 (1925); (b) M. Velghe, *Bull. Acad. Roy. Belg.*, **11**, 301 (1925).

[4] Since the over-all yields of the ketones from benzaldehyde were good, the method might be useful for the synthesis of certain substituted acylphenones through the alkylations of the appropriately substituted aromatic aldehydes.

TABLE I

ALKYLATION PRODUCTS II FROM α-AMINONITRILE I AND ALKYL HALIDES BY POTASSIUM AMIDE (EQUATION 1)

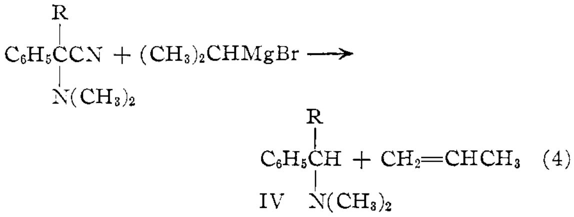
Product II, R	B.p., °C.	B.p., Mm.	$n^{25}D$	Yield, %	Calcd. for	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	98–100	6.3	1.5112	70	$C_{11}H_{14}N_2$	75.82	75.72	8.01	8.05	16.08	15.98
C_2H_5	89.5–89.8	1.2	1.5106	86	$C_{12}H_{16}N_2$	76.55	76.71	8.57	8.79	14.88	14.73
$CH(CH_3)_2$	99.5–100	1.7	1.5133	88	$C_{13}H_{18}N_2$	77.18	77.09	8.97	8.99	13.85	13.87
n-C_4H_9	108–108.5	1.5	1.5044	89	$C_{14}H_{20}N_2$	77.73	77.93	9.32	9.29	12.95	13.03

TABLE II

REACTION OF α-AMINONITRILES OF TYPE II WITH GRIGNARD REAGENTS TO FORM AMINES OF TYPE III (EQUATION 3)

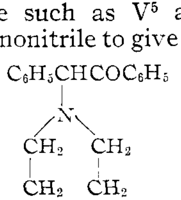
Expt.	R of II	R′ of R′MgX	Tertiary amine of type III	B.p. °C.	B.p. Mm.	$n^{25}D$ [a]	Yield,[b] %	Picrate m.p., °C.	Recovered II or ketone
1	CH_3	CH_3	2-Dimethylamino-2-phenylpropane (IIIa)	79–84[c]	8.7	1.5063	21	209–210	Acetophenone
2	C_2H_5	C_2H_5	3-Dimethylamino-3-phenylpentane (IIIb)	91–94	3.2–3.7	1.5152	77	149.5–151.5	Not isolated
3	CH_3	$C_6H_5CH_2$	1,2-Diphenyl-2-dimethylaminopropane (IIIc)	106	0.3	1.5600	81	159.5–160.5	Not isolated
4	$C_6H_5CH_2$	CH_3	1,2-Diphenyl-2-dimethylaminopropane (IIIc)			1.5600	Low	159.5–160.5	Desoxybenzoin
5	C_4H_9	CH_3	2-Dimethylamino-2-phenylhexane (IIId)	83–89	1.1–1.4	1.5043	78	152–153	Not isolated
6	CH_3	C_4H_9	2-Dimethylamino-2-phenylhexane (IIId)				0[d]		20–22% of II 46–60% acetophenone
7	C_4H_9	C_2H_5	3-Dimethylamino-3-phenylheptane (IIIe)	96–98.7	1.4–1.5	1.5083	85	103.5–105	5% valerophenone
8	C_2H_5	C_4H_9	3-Dimethylamino-3-phenylheptane (IIIe)	93–97	1.3–1.5	1.5083	62	103.5–105	21% propiophenone
9	$CH(CH_3)_2$	C_2H_5	2-Methyl-3-dimethylamino-3-phenylpentane (IIIf)	94–95	1.9–2.1	1.5182	58–69[e]	162–162.5	Isobutyrophenone
10	$CH(CH_3)_2$	C_4H_9	2-Methyl-3-dimethylamino-3-phenylheptane (IIIg)	111–113.5	2.2	1.5104	61[f]	154–156	Isobutyrophenone
11	C_2H_5	CH_3	2-Piperidino-2-phenylbutane (III′a)[g]	106–109[h]	1.55–1.7	1.5254	78	181–182	Not isolated
12	CH_3	C_2H_5	2-Piperidino-2-phenylbutane (III′a)[g]	104–108	1.4–1.55	1.5261	42	181–182	31% acetophenone

[a] Refractive index obtained from analytical samples of new compounds (Table IV). [b] The yield is based on aminonitrile I. [c] Reported b.p. 84–87° at 11 mm., $n^{25}D$ 1.5071, picrate m.p. 210–212° (A. C. Cope, T. T. Foster and P. H. Towle, THIS JOURNAL, **71**, 3929 (1949)). [d] The experiment was repeated several times but no amine of type III was obtained. [e] Two per cent. of reduction product 1-dimethylamino-1-phenyl-2-methyl propane isolated also. [f] Seven per cent. of reduction product above isolated also. [g] α-Piperidinophenylacetonitrile (I′) used instead of I. [h] Reported b.p. 288–290° at 760 mm., $n^{20}D$ 1.5233, chloroplatinate m.p. about 205° (P. Bruylants, *Bull. soc. chim. Belg.*, **33**, 467 (1924)). Found: chloroplatinate m.p. 196–197°. Picrate analysis: Calcd. for $C_{21}H_{26}N_4O_7$: C, 59.46; H, 5.78; N, 12.55. Found: C, 56.35; H, 5.77; N, 12.38.

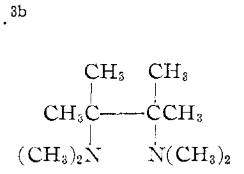


$$C_6H_5C(R)(N(CH_3)_2)CN + (CH_3)_2CHMgBr \longrightarrow \underset{IV}{C_6H_5CH(R)N(CH_3)_2} + CH_2{=}CHCH_3 \quad (4)$$

Two other courses of reaction reported previously in special cases, but not observed in the present work, involve the addition of the Grignard reagent to the nitrile group of the α-aminonitrile to form a ketone such as V[5] and the dimerization of the α-aminonitrile to give VI.[3b]



V



VI

In Tables II and III are summarized the results obtained from α-aminonitriles of type II with Grignard reagents to form tertiary amines of type III and IV, respectively. In both tables, the yields of the tertiary amines are based on aminonitrile I as the crude alkylation products were used; the over-all reaction is represented by equation 5.[6]

$$I \xrightarrow[2,\ RX]{1,\ KNH_2} II \xrightarrow{R'MgX} III \text{ or } IV \qquad (5)$$

Although excess of the Grignard reagent was employed[7] some of the α-aminonitrile II was generally present in the reaction mixture even after several hours at room temperature. The unreacted II was either recovered as such or as the corresponding ketone, which was produced through acid-catalyzed hydrolysis[8] (see equation 2). The

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(5) L. H. Goodson and H. Christopher, THIS JOURNAL, **72**, 358 (1950).

(6) Actually most of these experiments were performed before it was realized that the α-aminonitriles, in which R is alkyl, could be distilled readily without dehydrocyanation (see ref. 2). Later, it was shown that, in at least two cases, similar results are obtained employing purified samples of the α-aminonitriles II.

(7) On the basis that the reactions of α-aminonitriles of type II with Grignard reagents would involve one mole of each (see ref. 3) an estimated excess of 25–50% of the reagent was used.

(8) It is possible that the ketones arise partly from hydrolysis of intermediate enamines which might have been formed from β-eliminations by the Grignard reagents, since enamines also are converted to ketones by acid (see ref. 2).

TABLE III

REACTION OF α-AMINONITRILES OF TYPE I WITH GRIGNARD REAGENTS TO FORM AMINES OF TYPE IV (EQUATION 3)

Expt.	R of II	R′ of R′MgX	Tertiary amine of type III	B.p. °C.	B.p. Mm.	n^{25}D[a]	Yield,[b] %	Picrate m.p., °C.	Recovered II or ketone
1	C_4H_9	$C(CH_3)_3$	1-Dimethylamino-1-phenylpentane (IVa)	78	1.5–1.6	1.4963	71	159.5–160.5[c]	4% valerophenone
2	C_2H_5	$C(CH_3)_3$	1-Dimethylamino-1-phenylpropane (IVb)	73–76[d]	5.3–5.4	1.5016	46–56	166.5–167.5	Some II, propiophenone
3	C_2H_5	$CH(CH_3)_2$	1-Dimethylamino-1-phenylpropane (IVb)	77.5–79	7.3	1.5016	16–18	166.5–167.5	58% propiophenone
4	C_4H_9	$CH(CH_3)_2$	1-Dimethylamino-1-phenylpentane (IVa)	71–74	1.2	1.4966	23	159.5–160.5[c]	51% valerophenone
5	C_2H_5	$CH(C_3H_7)_2$	1-Dimethylamino-1-phenylpropane (IVb)	81–84	9.5	1.5050	3.5	166.5–167.5	Not isolated
6	$CH(CH_3)_2$	$CH(CH_3)_2$	1-Dimethylamino-1-phenyl-2-methylpropane (IVc)	62–64[e]	1.8–1.9	1.4996	76	166.5–167.5	19% of II 60% propiophenone

[a] Refractive index for IVa is for analytical sample. [b] Yields based on aminonitrile I. [c] Methiodide. [d] Reported b.p. 105–106° at 25 mm., n^{25}D 1.5002, picrate m.p. 165.5–166° (ref. 22). [e] Reported b.p. 80.5° at 1.0 mm., n^{25}D 1.4996, picrate m.p. 156–157° (ref. 14).

TABLE IV

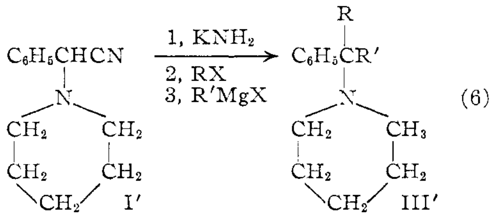
ANALYTICAL DATA[a] FOR NEW AMINES OF TYPES III AND IV AND THEIR PICRATES

		Amine analyses, %							Picrate analyses, %					
		C		H		N			C		H		N	
Cpd.	Calcd. for	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd. for	Calcd.	Found	Calcd.	Found	Calcd.	Found
IIIb	$C_{13}H_{21}N$	81.61	81.61	11.06	10.75	7.33	7.48	$C_{19}H_{24}N_4O_7$	54.58	54.28	6.09	5.75	13.29	13.33
IIIc								$C_{23}H_{24}N_4O_7$	58.97	58.81	5.16	5.30	11.96	12.01
IIId	$C_{14}H_{23}N$	81.88	81.85	11.29	11.21	6.82	6.78	$C_{20}H_{26}N_4O_7$	55.29	55.35	6.03	5.97	12.84	12.84
IIIe	$C_{15}H_{25}N$	82.09	81.95	11.84	11.44	6.38	6.38	$C_{21}H_{28}N_4O_7$	56.42	56.24	6.17	6.29	12.59	12.49
IIIf	$C_{14}H_{23}N$	81.88	81.97	11.29	11.19	6.82	6.85	$C_{20}H_{26}N_4O_7$	55.29	55.09	6.03	6.06	12.84	13.05
IIIg	$C_{16}H_{27}N$	82.33	82.58	11.66	11.95	6.00	6.19	$C_{22}H_{30}N_4O_7$	57.12	57.29	6.54	6.64	12.12	12.12
IVa	$C_{13}H_{21}N$	81.61	81.59	11.06	11.00	7.33	7.33	$C_{14}H_{24}NI$[b]	50.54	50.49	7.26	7.04	4.20	4.31

[a] Analytical samples obtained from center cuts on redistillation of amines. [b] In this instance the methiodide was prepared.

recovery of II or the ketone is given in the last columns of Tables II and III.

In the last two experiments in Table II, α-piperidinophenylacetonitrile (I′) was used instead of I leading to the formation of tertiary amines of type III′ (equation 6).

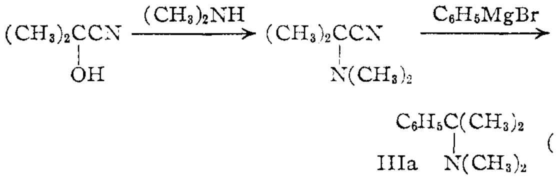


It can be seen from Table II that in each of the first two experiments the R group from the alkyl halide and the R′ group from the Grignard reagent were the same, but that in the remaining experiments the two groups were different. Although the experiment in which R and R′ were methyl gave tertiary amine IIIa in only 21% yield, that in which R and R′ were ethyl produced tertiary amine IIIb in 81% yield.

When the R group of the alkyl halide and the R′ group of the Grignard reagent were different the order of introduction of the groups appeared to be important. Thus experiments 3 and 4 both produced tertiary amine IIIc but the yield was high (81%) only when the methyl group was introduced in the alkylation, and the benzyl group in the Grignard reagent. The low yield when the benzyl group was introduced first must have been due to an unsatisfactory reaction of the benzylation product with methylmagnesium iodide, since the intermediate alkylation product was obtained in high yield.[2] However, in three other sets of experiments, the yield of the tertiary amine was favored when the larger alkyl group was introduced first. Thus, in the sets of experiments 5 and 6, 7 and 8, and 11 and 12, which produced tertiary amines IIId, IIIe and III′a, respectively, the highest yields were obtained when the larger alkyl group was introduced through the alkylation and the smaller group through the Grignard reaction.

It should be mentioned that in experiments 9 and 10 in Table II there was obtained, in addition to good yields of the corresponding amines of type III, a low yield of amines of type IV (see notes *e* and *f*, Table II). The latter type of amine is considered further below.

Two of the tertiary amines listed in Table II were known previously. They were identified in the usual manner by comparison of their physical constants. The structure of amine IIIa was further established by an independent synthesis employing the method of Perrine[9] (equation 7).



$$\underset{\mathrm{OH}}{(CH_3)_2\overset{|}{C}CN} \xrightarrow{(CH_3)_2NH} \underset{\mathrm{N(CH_3)_2}}{(CH_3)_2\overset{|}{C}CN} \xrightarrow{C_6H_5MgBr} \underset{\mathrm{N(CH_3)_2}}{C_6H_5\overset{|}{C}(CH_3)_2} \quad (7)$$

IIIa

The structure of III′a was further substantiated by the fact that it was obtained by introducing the methyl and ethyl groups into the α-aminonitrile I′ in the two ways considered above.

The other six tertiary amines listed in Table II were apparently new. Analysis for them and

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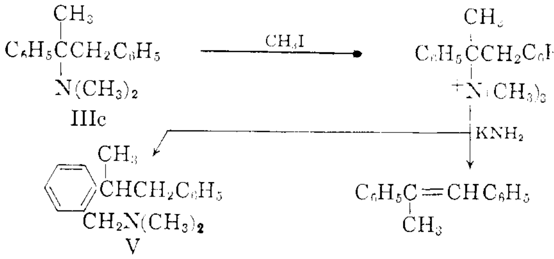
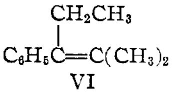
(9) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).

for their picrates or methiodides are given in Table IV. The structures of four of these amines are supported by the fact that they were prepared by the two possible modes of introduction of the R and R′ groups. Also, the methiodide of amine IIIc was treated with potassium amide in liquid ammonia to give partly α-methylstilbene and presumably the *ortho* substitution rearrangement product V (Scheme A). Although the amine product was not definitely established as V, this structure was supported by an infrared spectrum which showed, in addition to bands expected for a monosubstituted benzene ring, another strong band at 760 cm.$^{-1}$ indicative of an *o*-disubstituted benzene ring.[10] In addition, a band was present at 850 cm.$^{-1}$ which indicated the presence of a dimethylbenzylamine.[11]

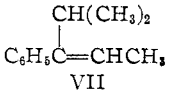
SCHEME A



It should be mentioned that, although tertiary amines IIIb and IIId appeared to form the methiodides on treatment with methyl iodide, the trimethylamino group was eliminated on recrystallization from chloroform and ether, only trimethylamine hydroiodide being isolated. Moreover, even tertiary amine IIIf, which has an isopropyl and an ethyl group, underwent deamination on refluxing it with acid overnight to form apparently a mixture of the olefins VI and VII[12,13] (see Experimental).


$C_6H_5C(CH_2CH_3){=}C(CH_3)_2$

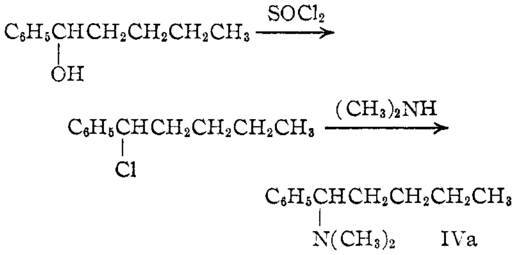
VI


$C_6H_5C(CH(CH_3)_2){=}CHCH_3$

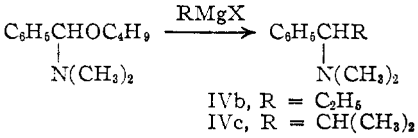
VII

It can be seen from Table III that treatment of α-aminonitriles of type II with Grignard reagents prepared from secondary or tertiary halides produced amines of type IV (equation 4) in yields of 4–76% based on the α-aminonitrile I (see equation 5). In the reactions of the ethyl and *n*-butyl alkylation products II, the yields were better with *t*-butylmagnesium chloride (expts. 1 and 2) than with isopropylmagnesium bromide (expts. 3 and 4) or 4-heptylmagnesium bromide (expt. 5). The best yield (76%) was obtained in the reaction of the isopropyl alkylation product II with isopropylmagnesium bromide (expt. 6). The analogous reaction with *t*-butylmagnesium bromide might be expected to produce an even better yield of the amine of type IV. None of the amines of type III were isolated in these reactions. In the experiments in which the yield of amines of type IV were low or fair, considerable amounts of the unreacted aminonitrile II evidently remained after the usual 3-hour period since good yields of the corresponding ketones were obtained on treatment of the reaction products with acid (see equation 2).

The structure of tertiary amine IVa was established by an independent synthesis from butylphenylcarbinol (equation 9).


$$C_6H_5CH(OH)CH_2CH_2CH_2CH_3 \xrightarrow{SOCl_2} C_6H_5CH(Cl)CH_2CH_2CH_2CH_3 \xrightarrow{(CH_3)_2NH} C_6H_5CH(N(CH_3)_2)CH_2CH_2CH_2CH_3 \quad \text{IVa} \qquad (9)$$

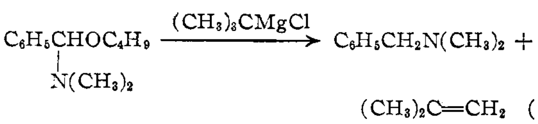
Tertiary amines IVb and IVc, which were known previously, were identified by comparison of physical properties and by an independent synthesis from α-dimethylaminobenzylbutyl ether and the appropriate Grignard reagent (equation 10).[14]


$$C_6H_5CH(N(CH_3)_2)OC_4H_9 \xrightarrow{RMgX} C_6H_5CH(N(CH_3)_2)R \qquad (10)$$

IVb, R = C_2H_5
IVc, R = $CH(CH_3)_2$

To substantiate the formation of the olefin from the Grignard reagent (see equation 4), this by-product was isolated and identified in two experiments. This was accomplished in the reaction of the isopropyl alkylation product II with isopropylmagnesium bromide by catching the propene in a Dry Ice–acetone trap and converting it to the dibromide (good yield). Similarly, in the reaction of the ethyl alkylation product with 4-heptylmagnesium bromide, the by-product 3-heptane was isolated as its dibromide.

While these hydride ion reductions appear to be the first reported with α-aminonitriles and Grignard reagents, an analogous reaction was observed previously in this Laboratory[14] with α-dimethylaminobenzylbutyl ether and *t*-butylmagnesium chloride (equation 11).


$$C_6H_5CH(N(CH_3)_2)OC_4H_9 \xrightarrow{(CH_3)_3CMgCl} C_6H_5CH_2N(CH_3)_2 + (CH_3)_2C{=}CH_2 \qquad (11)$$

(not isolated)

On the basis of the results described above, it would appear that the predominant course of re-

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[10] See L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1958.

[11] It has been observed in this Laboratory (C. R. Hauser and W. Q. Beard, unpublished results) that numerous N,N-dimethylbenzylamines show an absorption band in the 850 cm.$^{-1}$ region. This was found to be true of most of the amines in Tables II and III. However, the aminonitriles in Table I, which also possess the dimethylbenzylamine structure, did not exhibit this band in their spectra.

[12] A similar deaminative elimination of 1,1-diphenylethylamine to form α-phenylstyrene on refluxing the amine in acid solution has been observed by P. J. Hamrick and W. S. Owens of Wake Forest College; private communication from Dr. Hamrick.

[13] Amine IIIb, which has two ethyl groups, was recovered in 70% yield after similar treatment with acid.

[14] A. T. Stewart, Jr., and C. R. Hauser, THIS JOURNAL, **77**, 1098 (1955).

action of α-aminonitriles of type II with Grignard reagents is dependent mainly on the nature of the reagent, although the structure of the aminonitrile also has some effect. This is indicated in Table V. Since certain of these conclusions are based on only one or two reactions, they may be modified by future work.

TABLE V

OBSERVED COURSE OF REACTION OF α-AMINONITRILES OF TYPE II WITH GRIGNARD REAGENTS

R of aminonitrile II	R′ of Grignard reagent	Course of reaction observed
Primary	Primary	Replacement
Secondary	Primary	Mainly replacement (little reduction)
Primary	Secondary or tertiary	Reduction
Secondary	Secondary	Reduction

Experimental[15]

α-Dimethylaminophenylacetonitrile (I) was prepared from benzaldehyde, 25% aqueous dimethylamine and sodium cyanide as described previously[2] except that anhydrous dimethylamine was employed in the earlier procedure. The product boiled at 88–90° at 1.8–2.1 mm., yield 88%.

Alkylation of I with Ethyl Bromide to Form an Aminonitrile of Type II.—To a stirred suspension of 0.2 mole of potassium amide in 500 ml. of liquid ammonia[16] was added 32 g. (0.2 mole) of α-dimethylaminophenylacetonitrile (I). After 5 minutes 21.8 g. (0.2 mole) of ethyl bromide was added at a rate sufficiently slow to prevent excessive foaming. After two hours the ammonia was replaced by ether. After filtering the ethereal suspension, the ether was removed and the residue distilled to give 37.6 g. (86%) of α-dimethylamino-α-phenylbutyronitrile, b.p. 87–89.5° at 1.1–1.25 mm., $n^{25}\text{D}$ 1.5111. An analytical sample distilled at 89.5–89.8° at 1.2 mm., $n^{25}\text{D}$ 1.5106.

By a similar procedure, Compound I was methylated, isopropylated and butylated. These results are given in Table I.

Hydrolysis of Aminonitrile II to Form the Corresponding Ketone.—Thirty-four grams of the aminonitrile, obtained from the above alkylation, was refluxed in a hood (caution, hydrogen cyanide evolved) in a mixture of 50 ml. of hydrochloric acid and 200 ml. of water for 16 hours. The reaction mixture was cooled and extracted with three 100-ml. portions of ether. The ethereal extracts were washed with water and dried over anhydrous magnesium sulfate and filtered. After removal of the ether, the residue was distilled to give 20.4 g. of propiophenone boiling at 76–80° at 3.8–4.3 mm.,$n^{25}\text{D}$ 1.5255. The reported b.p. is 50° at 1 mm. and 77.9° at 5 mm.,[17] $n^{20}\text{D}$ 1.5270.[18] The semicarbazone melted at 171–173°; numerous references in the literature giving values from 170–180°. The infrared spectrum was identical with that of an authentic specimen.

In a similar manner, the methylated, isopropylated and butylated aminonitriles were hydrolyzed to the corresponding ketones in good, 74 and 83% yields, respectively. The identities of these ketones were established by the same methods employed with the propiophenone above.

General Procedure for the Reaction of Type II Aminonitriles with Grignard Reagents.—Alkylation of I was carried out as described above on a 0.2-mole scale. The crude product (after removal of the ether) was added dropwise to a stirred solution of the desired Grignard reagent, prepared from 0.3 mole of halide and 0.35 mole of magnesium in 500 ml. of ether. A vigorous reaction occurred as the aminonitrile was added and a thick pasty material formed, which soon solidified and caused some difficulty with stirring. After 3 hours, the solution was poured onto crushed ice and hydrochloric acid. The solid remaining in the flask was decomposed with more acid and added to the initial acid solution. After standing overnight, the ethereal layer was removed and the water layer extracted with two portions of ether. The combined ethereal solutions were washed with water and dried over anhydrous magnesium sulfate. After filtering, the ether was removed and the residue distilled to give varying yields of ketone.

The acidic solution was neutralized with ammonia and extracted with three 100-ml. portions of ether which were combined and washed with water. After drying over anhydrous magnesium sulfate, the solutions were filtered and the ether removed under reduced pressure. Fractionation of the residue gave the desired amines or unreacted aminonitrile II. The results and analytical data are contained in Tables II, III and IV.

In many cases some difficulty, due to excessive foaming was experienced in the distillation of the basic fraction. In the case of IIIa, the reaction mixture was allowed to stand in the acidic solution for 1 week in order to completely hydrolyze the unreacted II as it was difficult to fractionate these two materials.

Independent Synthesis of 2-Dimethylamino-2-phenylpropane.—This amine was synthesized from acetone cyanohydrin by conversion to the aminonitrile which was treated with phenylmagnesium bromide in accordance with the procedure of Perrine.[9] The infrared spectrum was superimposable on that of the amine obtained from aminonitrile II and a mixed m.p. of the picrates showed no depression.

Preparation of the Quaternary Salt of IIIc and Its Reaction with Potassium Amide.—To 50 ml. of acetonitrile was added 12 g. (0.05 mole) of 1,2-diphenyl-2-dimethylaminopropane (IIIc) and 14 g. of methyl iodide. After standing 4 hours, the solid mass was broken up and poured into 300 ml. of ether. The solid was thoroughly crushed and filtered. After drying in a vacuum, the salt was added to a solution of 0.13 mole of potassium amide in 300 ml. of liquid ammonia and allowed to stir for 3 hours. The dark color of the solution was discharged by the addition of wet ether and the ammonia then allowed to evaporate. The ethereal solution was stirred with 100 ml. of 2 *N* hydrochloric acid and the ether layer separated. The acid solution was extracted with two 100-ml. portions of ether which were combined with the original layer and washed with cold water. After drying over anhydrous magnesium sulfate, the solution was filtered and the solvent evaporated. The residue was taken up in a small amount of ether, treated with Norite and filtered. On cooling to −78° there was obtained 4.32 g. (45%) of α-methylstilbene, m.p. 78–79°, undepressed on admixture with an authentic sample. The infrared spectrum was identical with that of an authentic specimen.

The acid solution was neutralized with ammonia and extracted with three 100-ml. portions of ether. The ethereal extracts were washed with water, dried over anhydrous magnesium sulfate. filtered, and the solvent removed. Distillation of the residue gave 3.1 g. of liquid distilling at 136–139° at 0.45–0.50 mm., $n^{25}\text{D}$ 1.5570. The product analyzed correctly for 1-phenyl-2-(2-dimethylaminomethylphenyl)-propane.

Anal. Calcd. for $C_{18}H_{23}N$: C, 85.3; H, 9.15; N, 5.53. Found: C, 85.3; H, 9.16; N, 5.60.

The picrate, prepared and recrystallized from ethanol, melted at 135–138°.

Anal. Calcd. for $C_{24}H_{26}N_4O_7$: C, 59.74; H, 5.44; N, 11.62. Found: C, 59.57; H, 5.53; N, 11.71.

Attempted Preparation of the Methiodide of IIIb.—To a solution of 9.6 g. (0.05 mole) of 3-dimethylamino-3-phenylpentane in 30 ml. of acetonitrile was added 14 g. (0.10 mole) of methyl iodide. After standing for 4 hours, ether was added and the precipitated solid collected and dried, m.p. over 300°. The solid, recrystallized several times by dissolving in hot chloroform and precipitating with ether, slowly darkened 230–250°, more rapidly at 250–255° and melted 255–260° to a dark liquid. The reported m.p. for trimethylamine hydroiodide is 260° with prior darkening,[19]

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(15) Melting points were determined on a Fisher–Johns apparatus. All boiling points and melting points are uncorrected. Analyses carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained on a Perkin–Elmer model 21 instrument.

(16) See C. R. Hauser and T. M. Harris, THIS JOURNAL, **80**, 6360 (1958).

(17) See T. Earl Jordan, "Vapor Pressure of Organic Compounds," Interscience Publishers, Inc., New York, N. Y., 1954.

(18) O. Wallach, *Ann.*, **332**, 317 (1904).

(19) M. Delepine, *Ann. chim. phys.*, [7] **8**, 453 (1896).

and sublimes at 200°, darkens 251°, sinters 255°, and melts 263°.[20]

Anal. Calcd. for $C_3H_9N{\cdot}HI$: C, 19.25; H, 5.35; N, 7.48. Found: C, 19.43; H, 5.74; N, 7.44.

Similar results were obtained on attempting the preparation of the methiodide of IIId.

Deamination of IIIf.—Alkylation of I with isopropyl bromide and treatment of the product with ethylmagnesium bromide was carried out as described above. In order to remove any unreacted aminonitrile II from the product, the crude mixture was refluxed in hydrochloric acid solution for 16 hours. On working up in the usual manner, only a small amount of type IV amine was isolated and no type III amine, obtained in 58–69% yield in the general procedure described above. The neutral fraction was distilled to give 16.5 g. of liquid boiling at 67–73° at 4.0 mm. The infrared spectrum indicated the lack of either carbonyl or hydroxyl groups, but showed the presence of a double bond in conjugation with a phenyl group. The liquid decolorized bromine in carbon tetrachloride, slowly at first, but then rapidly, in agreement with the olefinic structures VI and VII.

Independent Synthesis of 1-Dimethylamino-1-phenylpentane.—Phenylbutylcarbinol (Eastman Kodak Co. white label) was converted to the chloride in 87% yield by a previously reported procedure.[21]

A solution of 25 g. of the chloride in 150 ml. of dry methanol was saturated with anhydrous dimethylamine and allowed to stand, under a drying tube, for 16 hours. The solution was then refluxed for 1 hour to remove the excess dimethylamine and the methanol was then removed under reduced pressure. The remaining slurry was taken up in dilute hydrochloric acid and extracted with ether to remove the neutral layer which formed. The acidic solution was made basic with solid sodium hydroxide, cooled, and extracted with three 100-ml. portions of ether. After drying over anhydrous magnesium sulfate and filtering, the ether was removed. The residue was distilled to give 16.4 g. (63%) of 1-dimethylamino-1-phenylpentane, b.p. 98–100° at 5.5 mm., $n^{25}D$ 1.4964. The infrared spectrum was identical with that of the product obtained from the aminonitrile and a mixed m.p. of methiodides showed no depression.

Independent Synthesis of 1-Dimethylamino-1-phenylpropane.—Five-hundredths of a mole (10.3 g.) of α-dimethylaminobenzyl butyl ether was treated with ethylmagnesium bromide in accordance with the previous procedure[14] to give 6.03 g. (73%) of 1-dimethylamino-1-phenylpropane, b.p. 81–82° at 9.3 mm., $n^{25}D$ 1.5007. The reported b.p. is 105–106° at 25 mm., $n^{25}D$ 1.5002.[22] The picrate melted at 166.5–167.5°, reported[22] 165.5–166. The infrared spectrum was identical with that of the product obtained from the aminonitrile and a mixed m.p. of the picrates showed no depression.

Independent Synthesis of 1-Dimethylamino-1-phenyl-2-methylpropane.—The previous procedure[14] was repeated to give a 65% yield of the amine, b.p. 61–62° at 1.8 mm., 77–78° at 4.1 mm., $n^{25}D$ 1.4998; picrate m.p. 156–157°; reported b.p. 80.5° at 1.0 mm., $n^{25}D$ 1.4996, picrate m.p. 156–157°. Due to the discrepancy in the b.p. the product was analyzed. The infrared spectrum was identical with that of the product obtained from the aminonitrile and a mixed m.p. of the picrates showed no depression.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.53; H, 10.83; N, 7.88.

Isolation of Olefin Derivatives from the Reaction of Grignard Reagents with Aminonitriles II.—The alkylation of α-dimethylaminophenylacetonitrile (I) was carried out with isopropyl bromide as described above and the crude product was added to a solution of isopropylmagnesium bromide in the usual manner. A Dry Ice–acetone trap was placed following the reflux condenser for the latter reaction. After completion of the addition of the nitrile and stirring for the desired time, the cold trap was removed and the contents quickly transferred to a three-necked flask equipped with a dropping funnel, stirrer and Dry Ice–acetone condenser. A solution of bromine in carbon tetrachloride was added dropwise (in the dark) until the persistence of the bromine color. The contents of the flask were fractionated to give a good yield of 1,2-dibromopropane boiling at 75–77° (pressure not recorded). The infrared spectrum was identical with that of an authentic sample.

In a similar reaction α-dimethylaminophenylacetonitrile (I) was alkylated with ethyl bromide and the crude product treated with 4-heptylmagnesium bromide. After decomposing the reaction mixture with hydrochloric acid, the neutral fraction was isolated and the heptane–heptene fraction boiling at 85–105° (mostly 94–100°) was collected. After treatment with bromine in carbon tetrachloride, the mixture was redistilled to give 4.9 g. (9.6%) of 3,4-dibromoheptane, b.p. 104–108° at 25 mm. The infrared spectrum was identical with that of an authentic specimen.

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[20] L. Wagner, *Z. Kryst. Mineral.*, **43**, 170 (1907).

[21] M. Protiva, J. Pliml, M. Borovicka and R. Rericha, *Chem. Listy*, **46**, 346 (1952). An infrared spectrum of our chloride indicated the presence of a carbonyl-containing impurity which was presumably the ketone corresponding to phenylbutylcarbinol.

[22] J. F. Bunnett, J. L. Marks and H. Moe, THIS JOURNAL, **75**, 985 (1953).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis and Some Reactions of Diazocyclobutane[1]

BY DOUGLAS E. APPLEQUIST AND DONALD E. MCGREER[2]

RECEIVED AUGUST 20, 1959

Diazocyclobutane has been prepared by the reaction of N-cyclobutyl-N-nitrosourea with alkoxides. The diazo compound forms cyclobutanone azine on thermal decomposition, cyclobutyl phenyl ketone on reaction with benzaldehyde, and a mixture of ethyl spirohexane-1-carboxylate and ethyl β-cyclobutylacrylates on reaction with ethyl acrylate. The reactions of the diazo compound with carboxylic acids in ether give mixtures of products which suggest both carbonium and oxonium ion intermediates. Cyclobutyl ethyl ether and cyclopropylcarbinyl ethyl ether are found as byproducts in the preparation of diazocyclobutane in ether–ethanol, and have been shown not to arise from diazocyclobutane.

Diazocyclobutane (I) appeared to be an important synthetic objective not only because of the paucity of knowledge about saturated secondary diazo compounds[3] and the lack of information on highly strained diazo compounds, but more specifically because Compound I appeared a likely source of the unknown trimethylenecarbene (II) and, in view of the non-classical behavior of the

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[2] Roger Adams Fellow, 1956–1957; Visking Corporation Fellow, 1957–1958.

[3] (a) H. Staudinger and A. Gaule, *Ber.*, **49**, 1897 (1916); (b) M. Lipp, *ibid.*, **74**, 1 (1941); (c) K. Heyns and A. Heins, *Ann.*, **604**, 133 (1957); (d) F. W. Bollinger, F. N. Hayes and S. Siegel, Abstracts of the 119th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1951, p. 87-M; (e) G. Hesse and E. Reichold, *Ber.*, **90**, 2101 (1957).