[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

SOME REACTIONS OF ω-DIALKYLAMINO-α,α-DIPHENYL-ALKANENITRILES

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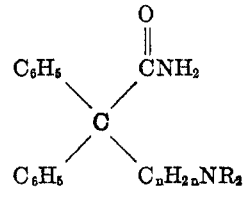
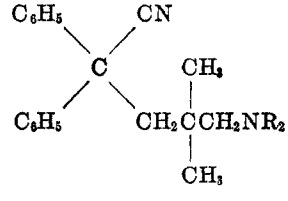
Consideration of certain irregularities in the reactions of a series of homologous nitriles led us to postulate steric effects as the main contributing factor. A series of basic amides was prepared by hydrolysis of the nitriles with 90% sulfuric acid (1), these amides being represented by the general formula I. The scope of this



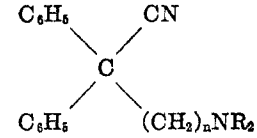
I

reaction was explored by varying n from two to five, including both straight and branched alkylene chains; the basic residue was varied to include cyclic and acyclic structures. The nature of the basic residue appeared to have no significant effect on the course of the hydrolysis; the effect of variation of the alkylene chain was indeed significant, as will be shown below.

The general experimental procedure used was to heat the nitrile with 90% sulfuric acid for about three hours on the steam-bath. In the large majority of cases, the yields of amides were good to excellent. Without exception, however,



II



III

a: $NR_2 = N(CH_3)_2$
b: $NR_2 = N(C_2H_5)_2$
c: $NR_2 = NC_5H_{10}$

nitriles represented by formula II were recovered unchanged under these conditions. Extension of the heating time to overnight (*ca.* 16 hours) resulted in a good conversion of such nitriles to amides. For example, IIc was converted to the amide in 69% yield on heating on the steam-bath for 16 hours; if only three hours heating were used, the nitrile was recovered to the extent of 86%. Nitriles containing straight carbon chains (III, n = 2, 3, 4, or 5) were hydrolyzed in good yields within three hours.

The Grignard reagent fails to add to nitriles of the type II, yet reacts normally with those lacking the *gem*-dimethyl moiety. The well-known methadone synthesis culminates in the reaction of ethylmagnesium bromide with 4-dimethylamino-2,2-diphenylvaleronitrile (2), and many related nitriles, including 5-dimethylamino-2,2-diphenylvaleronitrile (III, n = 3) (3), react with the same Grignard reagent, the expected ketone always being obtained. Two experiments in which IIc was treated with an excess of ethylmagnesium bromide, one in which a reaction temperature of 95° was maintained for 16 hours, resulted in isolation of starting material only. With the dimethylamino analog (IIa), a reaction occurred with ethylmagnesium bromide, but the reaction was one of decyanoation rather than addition to the cyano group. The product contained no oxygen, and was shown to be identical with the base obtained by heating the nitrile with potassium hydroxide in triethylene glycol, conditions under which decyanoation is known to occur (4). Decyanoation by means of a Grignard has been reported for 4,5-bis(dimethylamino)-2,2-diphenylvaleronitrile by Schultz (5), in unspecified yield. From IIa, 4-dimethylamino-3,3-dimethyl-1,1-diphenylbutane was obtained in 69% yield. Since this work was completed, additional examples of this type of reaction with the Grignard reagent have been reported (6).

These observations may be interpreted as a hindrance of approach of the attacking reagent toward the cyano group, and in particular toward the carbon atom of this group which is involved at some point in hydrolysis or addition of the Grignard reagent to the nitrile function (9, 10). Examination of Fisher-Hirschfelder-Taylor models of II and III shows that the two bulky phenyl groups require an attacking reagent to approach the carbon atom from the opposite side. In III, such an approach is unimpeded; in II the *gem*-dimethyl and dialkylaminomethyl system effectively shields the cyano group.

The effect of alkyl substitution in the carbon chain of aliphatic acids (or derivatives such as amides and nitriles) has been investigated enough so that certain generalizations have been made (7, 8, 11). As a general rule, the effect of methyl substitution is greatest in the β-position, next in the α- and least in the γ-position. However, the effect of substituents in any one position is modified by the presence of groups in other positions. The closest analogy to the reactions of II and III is to be found in the esterification of α-methylbutyric acid and α-methylneopentylacetic acid, in which the feeble steric hindrance of the γ-methyl groups is enhanced by the presence of the α-methyl.[1] It thus appears that the decrease in rate of hydrolysis and altered course of the Grignard reaction with II is a consequence of the γ-dimethyl substituents, acting in conjunction with the α-phenyl groups.

The variation in reactivity of the nitriles discussed represents small kinetic factors, particularly in relation to the magnitude of the variation of the esterification rates reported by Loening, Garrett, and Newman (8). However, these factors

[1] See ref. 8: Compare butyric acid, 3, to neopentylacetic acid, 10; and α-methylbutyric acid, 11, to α-methylneopentylacetic acid, 14; 3 and 10 are esterified at essentially the same rate, while 14 is esterified at a rate one-sixth that of 11. *Cf.* ref. 11: α,β,γ-trimethylhexadecanamide is hydrolyzed at a rate one-half that of α,β-dimethyloctadecanamide.

are of sufficient size to be significant in preparative organic chemistry, and do suggest that the relation of structure to reactivity in the aliphatic nitrile series needs clarification.

Acknowledgment. Several of the experiments reported herein were carried out by Dr. Merrill E. Speeter and by Messrs. William E. Fitzgibbon, Jr., and William F. Minor. Analyses were performed by Mr. Richard M. Downing. The author wishes to express his appreciation to Dr. Lee C. Cheney for his advice and encouragement.

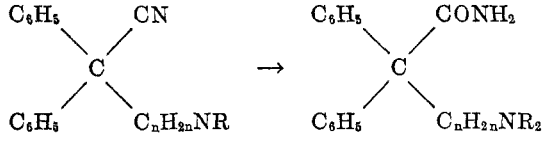
EXPERIMENTAL

Hydrolysis of dialkylaminoalkyldiphenylacetonitriles. This reaction has been previously described (1).

Table I summarizes the results of a number of these experiments, in which the basic nitriles were heated in 90% sulfuric acid on the steam-bath for the times indicated. The products were isolated by pouring the reaction mixtures into water and neutralizing with ammonium hydroxide.

Reaction of IIc with ethylmagnesium bromide. A solution of ethylmagnesium bromide was prepared in 250 ml. of anhydrous ether in the usual manner from 13.1 g. (0.12 mole) of ethyl bromide and 2.4 g. (0.1 mole) of magnesium turnings. To this solution was added dropwise a solution of 17.3 g. (0.05 mole) of IIc in a mixture of 150 ml. of xylene and 25 ml. of tetrahydrofuran (the nitrile is only slightly soluble in xylene, but quite soluble in tetrahydrofuran). Soon after the addition had been completed, the dark grey color of the reaction mixture faded to yellow. After five hours refluxing, the mixture was cooled and hydrolyzed with 100 ml. of saturated ammonium chloride solution. The organic layer was separated and shaken three times with sodium bisulfite solution, once with saturated sodium chloride, and filtered through anhydrous potassium carbonate. Distillation of the solvents left a solid residue, from which there was obtained 12.2 g. of IIc by crystallization from methanol; m.p. 65.0–66.0°, alone and when mixed with a sample of the starting material. This represents a 71% recovery of nitrile.

TABLE I



C_nH_{2n}	NR_2	REACTION TIME, hr.	PRODUCT	YIELD, %
$-CH_2CH_2-$	$-N(CH_3)_2$	2.5	Amide	82
$-CH_2CH(CH_3)-$	$-N(CH_3)_2$	3	Amide	84
$-CH_2CH_2CH_2-$	$-N(CH_3)_2$	2	Amide	74
$-CH_2C(CH_3)_2CH_2-$	$-N(CH_3)_2$	17	Amide	76
$-CH_2C(CH_3)_2CH_2-$	$-N(C_2H_5)_2$	3	Nitrile	47
$-CH_2C(CH_3)_2CH_2-$	$-N(C_2H_5)_2$	16	Amide	75
$-CH_2C(CH_3)_2CH_2-$	$-NC_5H_{10}$	3	Nitrile	86
$-CH_2C(CH_3)_2CH_2-$	$-NC_5H_{10}$	16	Amide	69
$-CH_2CH_2CH_2CH_2-$	$-NC_4H_8$	3.5	Amide	75

A second experiment was carried out with the same nitrile (IIc); the same solvent combination was used, and after the nitrile had been added, solvent was distilled until the vapor temperature reached 95°. The mixture was then refluxed for 16 hours, hydrolyzed and worked up as before. The only product identified was recovered nitrile.

4-Dimethylamino-3,3-dimethyl-1,1-diphenylbutane: reaction of IIa with ethylmagnesium bromide. The Grignard reagent was prepared in 200 ml. of anhydrous ether from 70.9 g. (0.65 mole) of ethyl bromide and 14.6 g. (0.6 mole) of magnesium turnings; after two hours refluxing all the magnesium had dissolved. The hydrochloride of IIa (68 g., 0.2 mole) was shaken with dilute potassium hydroxide and the liberated IIa was extracted with 200 ml. of xylene in three portions. The combined extracts were shaken with a saturated sodium chloride solution and were filtered through anhydrous sodium sulfate. Xylene was distilled until no more water appeared in the distillate. The dried solution of the nitrile was added over a period of one hour to the Grignard solution, and the reaction mixture was stirred and refluxed for 46 hours. The mixture was nearly black at the start, and remained so until the end of about 20 hours, at which time it suddenly turned olive-green. Hydrolysis was effected with ammonium chloride solution; the ether-xylene layer was separated, washed with saturated sodium chloride, and filtered through sodium sulfate. Removal of the solvents, followed by distillation *in vacuo*, gave 38.6 g. of colorless oil, b.p. 157°/1 mm., n_D^{25} 1.5436.

Anal. Calc'd for $C_{20}H_{27}N$: C, 85.4; H, 9.7; N, 5.6.
Found: C, 85.0; H, 9.6; N, 5.0.

The *hydrochloride*, recrystallized from methanol-ethyl acetate, melted at 182.5–184.0°.

Anal. Calc'd for $C_{20}H_{27}N \cdot HCl$: C, 75.6; H, 8.9.
Found: C, 75.3; H, 8.8.

The *picrate*, recrystallized from methanol, melted at 138.0–140.0°.

Anal. Calc'd for $C_{26}H_{30}N_4O_7$: N, 11.0. Found: N, 11.1.

4-Dimethylamino-3,3-dimethyl-1,1-diphenylbutane: reaction of IIa with potassium hydroxide. A solution of 12.3 g. (0.04 mole) of IIa and 12.3 g. of potassium hydroxide in 50 ml. of triethylene glycol (4) was stirred and refluxed for 12 hours. The cooled reaction mixture was poured into 300 ml. of water and extracted four times with ether. The combined ether extracts were shaken with saturated sodium chloride, filtered through anhydrous sodium sulfate, and the ether was evaporated. Distillation *in vacuo* gave 9.0 g. of colorless oil, b.p. 139–145°/0.5 mm., n_D^{25} 1.5422.

Anal. Calc'd for $C_{20}H_{27}N$: C, 85.4; H, 9.7.
Found: C, 85.2; H, 9.8.

The *hydrochloride*, alone and when mixed with the hydrochloride of the base obtained from the Grignard reaction, melted at 184.5–186.5°. Likewise, the picrate gave no depression of melting point when mixed with the picrate of the base from the Grignard reaction.

SUMMARY

5-Dialkylamino-4,4-dimethyl-2,2-diphenylvaleronitriles are resistant to acid hydrolysis and to the action of the Grignard reagent. These nitriles require a considerably longer time than the three hours which is sufficient to hydrolyze the straight chain ω-dialkylamino-2,2-diphenylalkanenitriles. Under ordinary conditions, ethylmagnesium bromide does not add to these nitriles; under drastic conditions, the 5-dimethylamino nitrile (IIa) is decyanoated to yield 4-dimethylamino-3,3-dimethyl-1,1-diphenylbutane in 69% yield. Potassium hydroxide-triethylene glycol decyanoation of the same nitrile proceeded in 87% yield.

These data indicate that the two γ-methyl groups, together with the two α-phenyl groups, provide steric hindrance to reactions at the nitrile function.

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