SYNTHESIS OF 4-CYANO-4-DIMETHYLAMINO-1,3-DIMETHYLPIPERIDINES AND 4-CYANO-4-DIMETHYL-1,2,5-TRIMETHYLPIPERIDINES AND INVESTIGATION OF FEATURES OF THEIR REACTIONS WITH SOME NUCLEOPHILIC REAGENTS

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4-Cyano-4-dimethylamino-1,3-dimethylpiperidines and 4-cyano-4-dimethylamino-1,2,5-trimethylpiperidines have been synthesized and the directions of their reactions with nucleophilic reagents (Grignard reagents, organolithium compounds, lithium tetrahydroaluminate, etc.) have been studied. Depending on the nature of the reagent, the reactions of the α-amino nitriles take place by addition to the cyano group, by its replacement, or by these two directions simultaneously.

The reaction of 4-cyano-4-dialkylaminopiperidines with Grignard reagents, organolithium compounds, and lithium tetrahydroaluminate has attracted attention in recent years as a simple and convenient method for obtaining physiologically active 4-monosubstituted and 4,4-disubstituted piperidine derivatives [1-5]. In the case of substituted 4-cyano-4-dialkylaminopiperidines, these reactions may lead to the formation of stereoisomeric compounds the physiological action of which must vary considerably according to their spatial structure. Up to the present time, the reactions of α-amino nitriles of the piperidine series with Grignard reagents, organolithium compounds, and lithium tetrahydroaluminate have been investigated only for the cases of the 1-benzyl-4-cyano-4-dialkylaminopiperidines and the 4-cyano-4-dialkylamino-2,2,6,6-tetramethylpiperidines [1-5], the structure of which excludes the possibility of the formation of stereoisomeric derivatives.

In order to elucidate the stereochemical laws of the reactions of substituted 4-cyano-4-dialkylaminopiperidines with Grignard reagents, organolithium compounds, and lithium tetrahydroaluminate and to obtain previously lacking information on their spatial directions, starting from 4-cyano-1,3-dimethyl- and 4-cyano-1,2,5-trimethylpiperidin-4-ols (I, II) [6, 7] we have synthesized 4-cyano-4-dimethylamino-1,3-dimethylpiperidines (III) and 4-cyano-4-dimethylamino-1,2,5-trimethylpiperidines (IV) and have studied the directions of their reactions with organomagnesium and organolithium compounds, with lithium tetrahydroaluminate, and with sodium in liquid ammonia. The amino nitriles (III, IV) were obtained by the reaction of the cyanohydrins (I, II) with methanolic dimethylamine [8].

According to the literature [9-12], the reactions of α-amino nitriles with organolithium and organomagnesium compounds may take place in three competing directions: at the nitrile carbon atom with addition to the triple bond of the cyano group (route A), at the α-carbon atom with the replacement of the cyano group by the radical of a Grignard reagent (route B), or with the hydrogenolysis of the $C_\alpha-N$ bond and the reductive replacement of the cyano group (route C). The relative reactivities of the two carbon atoms and, consequently, the predominant direction of the reaction depend both on the structure of the α-amino nitrile and on the nature of the organometallic reagent, a fundamental role being played by its nucleophilicity. The more nucleophilic organolithium compounds react predominantly by route A [10, 13-15], while the more electrophilic organomagnesium compounds react predominantly by route B [9-11]. The 4-cyano-4-dialkylaminopiperidines studied previously react with Grignard compounds only by route B [2, 4] and with organo-

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lithium compounds only by route A [2]. To determine the dependence of the direction of the reaction of the amino nitriles (III, IV) on the nature of the organomagnesium and organolithium reagents, we studied their reaction with a number of Grignard reagents (methyl-, tert-butyl-, and phenylmagnesium halides), methyl- and phenyllithiums, and lithium tetrahydroaluminate, and also sodium in liquid ammonia.

Investigation of the reaction products by the GLC method showed that, contrary to literature statements [2, 4], the reaction of the amino nitriles (III, IV) with methylmagnesium iodide does not take place only by route B, although the replacement of the nitrile group by the alkyl group of the Grignard reagent does take place predominantly. The amino nitrile (III) forms mainly 1,3,4-trimethylpiperidine (V) (97%) in admixture with the product of the reductive replacement of the cyano group by route C [4-dimethylamino-1,3-dimethylpiperidine (VI, 3%)]; and the amino nitrile (IV) gives 1,2,4,5-tetramethylpiperidine (VII, 93.5%) in admixture with the product of reductive substitution by route C [4-dimethylamino-1,2,5-trimethylpiperidine (VIII, 6.2%)] – and with the product of reduction by route A [4-acetyl-4-dimethylamino-1,2,5-trimethylpiperidine (IX, 0.3%)].

The reaction of the amino nitriles (III, IV) with tert-butylmagnesium chlorides takes place completely differently. Because of steric effects, the replacement of the cyano group by the radical of the Grignard reagent in accordance with route B proves to be impossible in this case, because of which the reductive replacement of the cyano group by route C takes place exclusively, with the formation of the aminopiperidines (VI) (99%) and (VIII) (100%).

The reaction of phenylmagnesium bromide with the amino nitrile (III), like the reaction with its cyclohexane analog [13, 14] takes place with the predominant formation of the product of replacement by route B [4-dimethylamino-1,3-dimethyl-4-phenylpiperidine (X, 54%)], obtained in admixture with the product of addition by route A [4-benzoyl-4-dimethylamino-1,3-dimethylpiperidine (XI, 33.8%)]. Similarly, the amino nitrile (IV) and phenylmagnesium bromide gave us a mixture of 4-dimethylamino-1,2,5-trimethyl-4-phenylpiperidine (XII, 72%) and 4-benzoyl-4-dimethylamino-1,2,5-trimethylpiperidine (XIII, 28%).

In contrast to these reactions, the reaction of the amino nitriles (III) and (IV) with the more nucleophilic phenyllithium, in agreement with the literature [16, 17], takes place mainly by route A and leads to the formation from the amino nitrile (III) of mainly the amino ketone (IX) (79%) in admixture with the amine (X) (21%), and the amino nitrile (IV), correspondingly, gave the amino ketone (XIII) (74%) in admixture with the amine (XII) (26%), formed like (X) with the replacement of the cyano group by a phenyl group. The main product of the reaction of methyllithium with the amino nitrile (III) is 4-acetyl-4-dimethylamino-1,3-dimethylpiperidine (XIV, 73%), and with the amino nitrile (IV) it is a mixture of the amino ketone (IX) (89.2%), the amine (VII) (9.8%), and the product of reductive substitution by route C – the amide (VII) (1%).

In the IR spectra of the amino ketones (XI and XIII) there is an intense absorption band characteristic for a benzene group at 1682 cm^{-1}, and in the spectra of their aliphatic analogs (IX and XIV) the absorption band of the carbonyl of an acetyl group is found at 1725 cm^{-1} [18]. If the hydrolysis of the products of the reaction of the amino nitriles (III) and (IV) with organolithium compounds is performed not in dilute hydrochloric acid but with an aqueous solution of ammonia or ammonium chloride, the corresponding ketimines are obtained. Thus, from the amino nitrile (III) and phenyllithium we obtained the corresponding ketimine [4-benzimidoyl-4-dimethylamino-1,3-dimethylpiperidine (XV)].

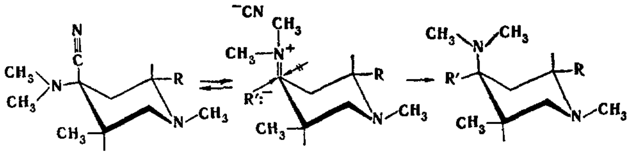
In the reaction of the amino nitriles (III, IV) with lithium tetrahydroaluminate, it was also possible to expect the formation both of the product of addition to the cyano group with the formation of an aminomethyl derivative (route A), the product of reductive dimerization (route B), and also the product of hydrogenolysis with the splitting out of the cyano group and its replacement by a hydrogen atom (route C) [9, 10]. The main direction of the reaction according to the literature [9, 10] in this case depends on the structure of the α-amino nitrile. Under the action of lithium tetrahydroaluminate, the previously described 4-cyano-4-dialkylaminopiperidines undergo hydrogenolysis by route C exclusively with the formation of 4-dialkylaminopiperidines of the type of the amines (VI, VIII) [3, 5]. In contrast to literature information [3, 5], we have established that the direction of the reaction of the amino nitriles (III, IV) with lithium tetrahydroaluminate depends not only on their structure but, and primarily, on the conditions of performing the reaction (temperature, etc.). Thus, for example, the amino nitrile (III) on being boiled with a suspension of lithium tetrahydroaluminate (1 : 2), reacts simultaneously in both possible directions, but the hydrogenolysis process is sharply predominating. At the same time, the product of reductive replacement by route C – the amine (VI) (87%) – is formed in admixture with the product of addition to the cyano group by route A [4-aminomethyl-4-dimethylamino-1,3-dimethylpiperidine (XVI, 13%)]. A reduction in temperature leads to an increase in the role of the reaction involving the reduction of the cyano group by route A and to a decrease in the degree of reductive substitution of the amino nitrile (III) by route C. At the same time, the amino nitrile (IV) reacts with lithium tetrahydroaluminate (ratio of the reactants 1:2) at 0°C with the formation predominantly of the product of hydrogenolysis by route C – the amine (VIII) (68.8%).

The reaction of the amino nitrile (III) with lithium tetrahydroaluminate at a temperature of –20°C takes place with the formation of a mixture of products of addition by route A – the amine (XVI) (23%) – of reductive dimerization by route B [bis(4-dimethylamino-1,3-dimethylpiperidin-4-yl)methylamine (XVII, 49.5%)] and of reductive substitution by route C – the amine (VI) (26.7%). The quantitative ratio of the amines (VI), (XVI), and (XVII) depends on the temperature. Thus, for example, in the reduction of the amino nitrile (III) at 0°C, in the mixture of products formed the proportion of the amines (XVI) and (VI) rises and the relative amount of the product of reductive dimerization – the amine (XVII) – falls.

With the amino nitrile (IV) as an example, we have shown that the elimination of the cyano group with the aid of tert-butylmagnesium chloride and lithium tetrahydroaluminate can also readily be effected by the action of a solution of sodium in liquid ammonia. This reaction, which is apparently similar in its nature to the decyanation of α-dialkylamino nitriles by boiling them with sodium in toluene [19], leads to the formation of the amine (VIII) exclusively, and is completely unaccompanied by the dimerization exchange observed by Thies et al. [19] or by the reduction of the cyano group found previously in the reaction of some α-dialkylamino nitriles with sodium amalgam in moist ether [20].

By means of TLC and GLC we have established that all the reactions of the amino nitriles (III) and (IV) that have been studied are strictly stereospecific and take place with the formation of only one geometric isomer of the product of addition by route A or of the replacement of the cyano group by routes B and C.

The spatial directedness of the replacement of the cyano group of an amino nitrile (III) or (IV) by the radical of a Grignard reagent by route B and their reductive replacement by route C during their hydrogenolysis according to the literature [9, 12, 13, 21-23], is connected with the mechanisms of these reactions. According to the literature sources cited, the reactions of α-dialkylamino nitriles with Grignard reagents by routes B and C and with lithium tetrahydroaluminate by route C takes place by an S_N1 monomolecular nucleophilic substitution mechanism with the formation of an intermediate immonium cation. In these circumstances, attack of the double bond of the immonium cation by the nucleophile takes place predominantly from the less sterically hindered equatorial region [13], i.e., analogously to the attack by a Grignard reagent of the double bond of the carbonyl group of six-membered cyclic ketones [24, 25]. As a result of this spatial directedness of the reactions, in the case of the stereoisomers of 4-tert-butyl-4-cyano-1-dialkylaminocyclohexane, regardless of their configurations, the main reaction product obtained is the cis isomer of 4-tert-butyl-1-dialkylaminocyclohexane with the equatorial orientation of the entering substituent (H, R, C_6H_5) and with an axial dimethylamino group.*



III R=H; IV R=CH_3 $\quad$ R'=H, R, C_6H_5

In agreement with these results, the individual geometric isomers of the aminopiperidines (V, VII, X, and XII) obtained from the amino nitriles (III) and (IV) have a spatial structure with an axial dimethylamino group and with the trans position of the 3-CH_3 equatorial group in compounds (V) and (X) and of the 5-CH_3 group in their analogs (VII) and (XII), and equatorial 4-CH_3 or 4-C_6H_5 groups, which agrees with conclusions given in the literature [22, 23, 26] on the spatial structure of carbocyclic analogs of compounds (VII) and (XII). In their turn, the reactions of the reductive substitution of the amino nitrile (IV) by route C on reaction with tert-butylmagnesium chloride, lithium tetrahydroaluminate, and sodium in liquid ammonia and the hydrogenolysis of the amino nitrile (III) with lithium tetrahydroaluminate, which have similar mechanisms, should, because of the similar natures of the stereodirectedness of the reactions, lead to the formation of the geometric isomers of the amine (VI) from the amino nitrile (III) and of the amine (VIII) from the amino nitrile (IV), with an axial dimethylamino group present in the cis position relative to the

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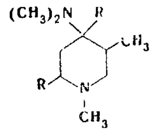
*We shall describe the determination of the spatial structures of the compounds obtained in a later communication.

TABLE 1



Comp.	R	R′	bp, °C (pressure, mm)	n_D^{20}	R_f	Empirical formula	Found, %			Calc., %			Yield, %
							C	H	N	C	H	N	
V	H	CH_3	65—66 (0,5)	1,4675[b]	0,51	$C_{10}H_{22}N_2$	70,0	12,8	15,8	70,6	13,0	16,4	68
X	H	C_6H_5	mp 76—77[a]	—	0,32	$C_{15}H_{24}N_2$	77,5	10,7	11,6	77,6	10,4	12,1	54
VI	H	H	46—47 (0,5)	1,4660[b]	0,33	$C_9H_{20}N_2$	69,7	13,2	18,1	69,2	12,9	17,9	99
XIV	H	$COCH_3$	110—112 (30)	1,4730	0,45	$C_{11}H_{22}N_2O$	66,3	11,4	14,1	66,5	11,2	14,2	73
XI	H	COC_6H_5	136—138 (4)	—	0,24	$C_{16}H_{24}N_2O$	74,2	9,3	10,9	74,0	9,1	10,7	79
VII	CH_3	CH_3	77—78 (2)	1,4729	0,57	$C_{11}H_{24}N_2$	71,3	13,0	15,1	71,7	13,1	15,2	89
XII	CH_3	C_6H_5	mp 75—76[a]	—	0,48	$C_{16}H_{26}N_2$	78,2	10,4	11,5	78,0	10,6	11,4	76
VIII	CH_3	H	54—55 (4)	1,4643	0,35	$C_{10}H_{22}N_2$	70,4	13,2	16,5	70,5	13,1	16,5	65
IX	CH_3	$COCH_3$	87—89 (15)	1,4911	0,38	$C_{12}H_{24}N_2O$	68,5	10,9	13,1	68,0	11,3	13,2	89
XIII	CH_3	COC_6H_5	131—132 (3)	1,5358	0,28	$C_{17}H_{26}N_2O$	74,3	9,3	10,4	74,4	9,5	10,2	28
XV	H	$C(=NH)C_6H_5$	mp 121—122[a]	—	—	$C_{16}H_{25}N_3$	73,7	9,9	16,0	74,0	9,7	16,2	82

[a] From hexane. [b] At 18°C.

3-CH_3 group of the amino nitrile (III) and to the 5-CH_3 group of its analog (IV). The presence in each of the amino nitriles (III) and (IV) of two nitrogen atoms favors the appearance in the reaction process of cyclic transition complexes of the chelate type with the participation of the metal atom of the organometallic compound and of the lithium tetrahydroaluminate, which explains the strict stereodirectedness of the reactions of the replacement of the cyano group by routes B and C as compared with their carbocyclic analogs.

At the same time, nucleophilic addition to the triple bond of the nitrile group of the amino nitriles (III) and (IV) by route A takes place without their epimerization and, because of this, leads likewise to the formation of individual geometric isomers of the amino ketones (IX, XI, XIII, and XIV) or of the primary amine (XVI) having the configurations of the initial compounds [23]. According to the literature [27, 28] on the spatial structure of the carbocyclic α-amino nitriles, it is most likely that the amino nitriles (III) and (IV) have, just like these compounds, a configuration with an equatorial arrangement of the dimethylamino group and an axial orientation of the cyano group. In this case, the amino ketones (IX, XI, XIII, and XIV) must be assigned a spatial structure with an axial acyl group, and the amine (XVI) the configuration with an axial aminomethyl grouping present in the cis position relative to the neighboring 3- or 5-CH_3 group.

EXPERIMENTAL

Analytical GLC was performed on an LKhM-7A chromatograph with a katharometer detector, a stainless-steel column (4 × 1000 mm), with 10% of polyethyleneglycol (mol. wt. 10,000) on Celite as the stationary phase and helium as the carrier gas at a rate of flow of 60-62 ml/min, and at a temperature of 150°C. TLC was performed on plates with non-fixed Al_2O_3 of activity grade II in the diethyl ether–petroleum ether (3 : 1) system, the spots being revealed with iodine vapor.

The purification of the compounds synthesized was performed by preparative separation of the components of the reaction mixtures on columns 1.5 m long and 15 mm in diameter filled with alumina of activity grade II using as eluents petroleum ether followed by mixtures of petroleum ether with diethyl ether with gradually increasing proportions of the latter.

4-Cyano-4-dimethylamino-1,3-dimethylpiperidine (III). Gaseous dimethylamine was passed into a solution of 15.4 g (0.1 mole) of 4-cyano-1,3-dimethylpiperidin-4-ol (I) [7] in 300 ml of methanol until the increase in the weight was 13.5 g (0.3 mole), after which the reaction mixture was left at room temperature for three days. The methanol was driven off in a gentle vacuum at 20°C, and the oily residue was distilled. This gave 15.93 g (88%) of the amino nitrile (III) in the form of a colorless oil with bp 68.5-69°C (2 mm); n_D^{20} 1.4775; d_4^{20} 0.9647. Found, %: C 66.6; H 10.5; N 23.4; MR_D 53.13. $C_{10}H_{19}N_3$. Calculated, %: C 66.2; H 10.6; N 23.2; MR_D 53.56.

4-Cyano-4-dimethylamino-1,2,5-trimethylpiperidine (IV). This was obtained in a similar manner to the amino nitrile (III). Yield 92%. bp 79-82°C (1.5 mm); n_D^{20} 1.4771; d_4^{20} 0.9516.

Found, %: C 67.7; H 10.9; N 21.6; MR_D 57.99. $C_{11}H_{21}N_3$. Calculated, %: C 67.6; H 10.8; N 21.5; MR_D 57.73.

Reactions of 4-Cyano-4-dimethylamino-1,3-dimethylpiperidine (III) and 4-Cyano-4-dimethylamino-1,2,5-trimethylpiperidine (IV).* With Methylmagnesium Iodide. A. With stirring, a solution of 5 g (0.03 mole) of the amino nitrile (III) in 10 ml of dry ether was added over 1 h to a solution of the methylmagnesium iodide obtained from 2.7 g (0.1 g-atom) of magnesium and 15.6 g (0.1 mole) of methyl iodide in 50 ml of dry ether. The reaction mixture was heated at a gentle boil for 6 h, cooled to room temperature, and hydrolyzed with 100 ml of dilute (1 : 1) hydrochloric acid. The ethereal layer was separated off and the acidic aqueous layer was boiled for 1 h, cooled to room temperature, neutralized and saturated with potassium carbonate, the oil that separated out was extracted with ether (3 × 50 ml), the ethereal extracts were dried with magnesium sulfate, and the ether was evaporated off, to give 3.8 g of an oily product containing, according to GLC, 97% of 4-dimethylamino-1,3,4-trimethylpiperidine (V) and 3% of 4-dimethylamino-1,3-dimethylpiperidine (VI). After vacuum distillation, 3.1 g of the amine (V) and 0.6 g of the amine (VI) were obtained. For analysis, the amines obtained were purified on a chromatographic column of alumina using diethyl ether–petroleum ether (1 : 9) as eluent.

B. The reaction of an ethereal solution of methylmagnesium iodide obtained from 3 g (0.11 g-atom) of magnesium and 17.5 g (0.37 mole) of methyl iodide in 100 ml of dry ether with an ethereal solution of 5 g (0.03 mole) of the amino nitrile (IV) in 10 ml of dry ether, after the performance of the process and working up as described above, yielded 4.7 g of an oily substance containing, according to GLC, 93.8% of 4-dimethylamino-1,2,4,5-tetramethylpiperidine (VII), 6.2% of 4-dimethylamino-1,2,5-trimethylpiperidine (VIII), and 0.3% of 4-acetyl-4-dimethylamino-1,2,5-trimethylpiperidine (IX). Vacuum distillation yielded 0.4 g of the amine (VIII) [picrate, mp 197-197.5°C (decomp., from 50% ethanol)] and 4.2 g (89%) of the amine (VII) [picrate, mp 210-211°C (from 70% ethanol)].

With Phenylmagnesium Bromide. A. The reaction of an ethereal solution of phenylmagnesium bromide obtained from 3.1 g (0.13 g-atom) of magnesium and 21.8 g (0.14 mole) of bromobenzene in 50 ml of dry ether with a solution of 5.0 g (0.03 mole) of the amino nitrile (III) in 10 ml of dry ether gave, after working up as described above, 8.7 g of an oily product which soon partially crystallized. After washing with ether, 4.3 g (54%) of 4-dimethylamino-1,3-dimethyl-4-phenylpiperidine (X) was obtained; picrate, mp 209-209.5°C (decomp., from 50% ethanol). Vacuum distillation of the filtrate yielded 1.0 g (12%) of 1,3-dimethylpiperidin-4-one with bp 43-45°C (2 mm), n_D^{20} 1.4560; and 2.8 g (34%) of 4-benzoyl-4-dimethylamino-1,3-dimethylpiperidine (XI).

B. The reaction of a solution of phenylmagnesium bromide prepared from 6 g (0.25 g-atom of magnesium and 39 g (0.25 mole) of bromobenzene in 100 ml of dry ether with 10.2 g (0.06 mole) of the amino nitrile (IV) after the performance of the process and working up as described above, gave 6.8 g (76%) of 4-dimethylamino-1,2,5-trimethyl-4-phenylpiperidine (XII), bp 123-124°C (4 mm); n_D^{20} 1.5360 [picrate, mp 194-195°C (decomp., from 50% ethanol)], and 2.2 g (24%) of 4-benzoyl-4-dimethylamino-1,2,5-trimethylpiperidine (XIII); picrate, mp 168-169°C (decomp., from 50% ethanol).

With tert-Butylmagnesium Chloride. A. A solution of 5 g (0.03 mole) of the amino nitrile (III) in 10 ml of dry ether was added dropwise to a solution of the tert-butylmagnesium chloride prepared from 2.9 g (0.1 g-atom) of magnesium and 11 g (0.12 mole) of tert-butyl chloride in 30 ml of dry ether. After the performance of the reaction and working up as described above, 4.9 g of an oily product was obtained which, according to GLC, contained 99% of 4-dimethylamino-1,3-dimethylpiperidine (VI). After vacuum distillation and purification on a chromatographic column containing Al_2O_3, 4.7 g of the amine (VI) was obtained.

B. The reaction of a solution of tert-butylmagnesium chloride prepared from 0.6 g (0.021 g-atom) of magnesium and 1.86 g (0.02 mole) of tert-butyl chloride in 30 ml of dry ether, with a solution of 2 g (0.015 mole) of the amino nitrile (IV) under the conditions of the preceding experiment, after working up as described above, gave 1.3 g of the amine (VIII) as the sole product according to GLC. After vacuum distillation, 1.1 g (65%) of the amine (VIII) was obtained with d_4^{18} 0.8758; n_D^{18} 1.4660; MR_D 53.86, calculated 53.76. Picrate, mp 197-197.5°C (decomp., from 50% ethanol); a mixture with a sample of the picrate of the amine (VIII) from the preceding experiments gave no depression of the melting point.

With Methyllithium. A. The reaction of 5 g (0.03 mole) of the amino nitrile (III) with the methyllithium, obtained from 5 g (0.7 g-atom) of lithium and 61 g (0.43 mole) of methyl iodide in 100 ml of ether, after heating for 4 h at a gentle boil, cooling to room temperature, hydrolysis with 40 ml of dilute (1 : 1)

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*The characteristics of the reaction products are given in Table 1.

hydrochloric acid, and working up as described above, gave 3.9 g (73%) of 4-acetyl-4-dimethylamino-1,3-dimethylpiperidine (XIV).

B. The reaction of a solution of methyllithium prepared from 1.7 g (0.24 g-atom) of lithium and 17.5 g (0.12 mole) of methyl iodide in 50 ml of dry ether with 5 g (0.03 mole) of the amino nitrile (IV) under the conditions of the preceding experiment, after working up as described above, gave 4.6 g of an oily product containing, according to GLC, 89% of the amino ketone (IX), 9.8% of the amine (VII), and 1.0% of the amine (VIII). After vacuum distillation, a third fraction yielded 4.4 g (80%) of the amino ketone (IX).

With Phenyllithium. A. To a solution of phenyllithium obtained from 2.1 g (0.3 g-atom) of lithium and 21.8 g (0.14 mole) of bromobenzene in 100 ml of dry ether was added 5 g (0.03 mole) of the amino nitrile (III). After the performance of the reaction and working up as described in the preceding experiment, 9.8 g of an oily substance was obtained which soon partially crystallized. The crystalline product was separated from the oil by washing with hexane on the filter. This gave 1.7 g (21%) of the amine (X), giving no depression of the melting point in admixture with a sample of the amine (X) obtained by the reaction of the amino nitrile (III) with phenylmagnesium bromide. After vacuum distillation, the filtrate yielded 8.1 g (80%) of the amino ketone (XI), which, after chromatography on a column of Al_2O_3, proved to be identical with the product obtained by the reaction of the amino nitrile (III) with phenylmagnesium bromide.

B. The same amounts of starting materials, after hydrolysis with 50 ml of a 26% aqueous ammonia solution, extraction with ether, and the usual working up, yielded 9.2 g (82%) of 4-benzimidoyl-4-dimethylamino-1,3-dimethylpiperidine (XV), which, after being boiled with concentrated hydrochloric acid was converted into the amino ketone (XIII), identical with that described in the preceding experiments.

C. A solution of 9.5 g (0.057 mole) of the amino nitrile (IV) in 20 ml of dry ether was added dropwise to a solution of phenyllithium prepared from 8 g (0.05 mole) of bromobenzene and 0.7 g (0.1 g-atom) of lithium in 100 ml of dry ether. The reaction mixture was heated at a gentle boil for 5 h and was hydrolyzed with 100 ml of ice water and 20 ml of concentrated hydrochloric acid with cooling. The acid layer was separated off, the ethereal layer was washed with water, and the combined aqueous extracts were heated at 50°C for 4 h. The acid solution was concentrated in vacuum to one-third of its initial volume, neutralized, and saturated with caustic soda, and the base was extracted with ether. After the elimination of the solvent, the residue was distilled in vacuum, giving a viscous yellow oil which was separated on a chromatographic column of alumina using isooctane and mixtures of isooctane and chloroform as eluents. This gave 6.8 g (74%) of the amino ketone (XIII), bp 131-132°C (3 mm); n_D^{20} 1.5358 and 2.3 g (26%) of the amine (XII) with mp 77-78°C (from hexane) which proved to be identical with the samples of the amine (XII) obtained in the preceding syntheses. The picrate, mp 168-169°C (from ethanol), gave no depression of the melting point in admixture with a sample of the same compound obtained from the amino nitrile (IV) and phenylmagnesium bromide. The amine (XII) and the amino ketone (XIII) were additionally purified on columns of Al_2O_3.

With Lithium Tetrahydroaluminate. A. A solution of 5 g (0.03 mole) of the amino nitrile (III) in 10 ml of dry ether was added to a suspension of 0.4 g (0.06 mole) of lithium tetrahydroaluminate in 30 ml of dry ether. The mixture was boiled moderately for 4 h, cooled to room temperature, hydrolyzed with 40 ml of saturated caustic potash solution, and extracted with 150 ml of ether. The ethereal extracts were dried with magnesium sulfate. After the ether had been distilled off, 5.1 g of an oily substance containing, according to GLC, 87% of the amine (VI) and 13% of the amine (XV) was obtained. Vacuum distillation yielded 3.3 g of the amine (VI), the picrate of which gave no depression of the melting point in admixture with a sample of the picrate of the amine (VI) obtained in the preceding experiments.

B. A solution of 5 g (0.03 mole) of the amino nitrile (III) in 50 ml of ether was slowly added to a suspension of 0.4 g (0.06 g-atom) of lithium aluminum hydride in dry ether cooled to −20°C. The reaction mixture was stirred at the same temperature for 5 h and was then hydrolyzed with 25 ml of 20% caustic soda. After working up as described in the preceding experiment, 5.11 g of an oil was obtained which, according to GLC, contained 24.0% of 4-amino-4-dimethylamino-1,3-dimethylpiperidine (XVI), 27.0% of the amine (VI), and 44.5% of bis(4-dimethylamino-1,3-dimethylpiperidin-4-yl)methylamine (XVII). Vacuum distillation gave the amine (VI) with bp 46-47°C (0.5 mm), the amine (XVI) [bp 82-82.5°C (1.5 mm); n_D^{20} 1.4923; d_4^{20} 0.9383. Found, %: C 64.9; H 12.3; N 22.7; MR_D 57.31. $C_{10}H_{23}N_3$. Calculated, %: C 64.7; H 12.6; N 22.7; MR_D 57.19], and 0.9 g of the amine (XVII), bp 153-155°C (1.5 mm); n_D^{20} 1.5080. Found, %: C 68.3; H 12.1; N 19.8. $C_{20}H_{43}N_5$. Calculated,%: C 67.9; H 12.37; N 19.8. For additional purification, the amines (XVI) and (XVII) were chromatographed on a column of Al_2O_3.

C. With stirring, a solution of 5 g (0.03 mole) of the amino nitrile (III) in 25 ml of ether was added over 50 min to a suspension of 0.4 g of lithium tetrahydroaluminate in 200 ml of dry ether cooled to 0°C in such a way that the temperature of the reaction mixture did not rise above 0°C. The mixture was kept at 0°C for 5 h, after which it was hydrolyzed with 20 ml of 20% caustic soda, the ethereal layer was decanted from the pasty mass, which was washed with ether five more times, and the ethereal extracts were combined. Distillation of the solvent gave an oily residue containing, according to GLC, 69.0% of the amine (VI) and 31.0% of the amine (XVI). The separation of the amines (VI) and (XVI) was performed as described in the preceding experiment.

With Sodium in Liquid Ammonia. In drops, 19.5 g (0.1 mole) of the amino nitrile (IV) was added to a solution of 4.6 g (0.2 g-atom) of sodium in 250 ml of liquid ammonia cooled to −60°C, and then, after 20 min, 50 ml of anhydrous ethanol was added (to decompose the sodium amide). The reaction mixture was left overnight. On the following day, 50 ml of water was added and it was acidified with dilute hydrochloric acid (1 : 1). After the elimination of the ethanol in a gentle vacuum, the acid solution was twice extracted with ether to remove neutral products. It was then saturated with caustic soda and again extracted with ether. The solvent was driven off and the residue was distilled in vacuum to give 12.4 g (73%) of an oil which, according to GLC, contained 100% of the amine (VIII). Picrate, mp 196-197°C (from 50% ethanol). A mixture with picrates of samples of the amine (VIII) obtained in the preceding experiments gave no depression of the melting point.

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