chloride. Recrystallization from methanol gave the pure sample, mp 195–196°.

Treatment of the free enol **16** with pyridine–acetic anhydride (3:1) instead of pyridine alone gave an essentially identical crude product as evidenced by its ultraviolet spectrum and by thin layer chromatography. Isolation of pure 8,19-oxide **11** was accomplished by chromatography and recrystallization, while identity was established by comparison of infrared spectra.

Deconjugation of 1 and 3 in the Presence of Methanol.—A mixture of 4 g of sodium methoxide, 10 ml of dimethyl sulfoxide, and 10 ml of cosolvent, consisting of varying amounts of methanol and tetrahydrofuran, was stirred in an ice bath and in an atmosphere of prepurified nitrogen until it had cooled down to a temperature of 2–3°. A solution of 1.66 mmol of **1** (500 mg) or of **3** (473 mg) in a mixture of 10 ml of dimethyl sulfoxide and 10 ml of cosolvent was cooled to 2° and then added to the basic reaction mixture in one portion. The temperature of the stirred mixture was maintained at 2–3° for 5 min whereupon 100 ml of benzene and a freshly prepared mixture of 20 ml of concentrated hydrochloric acid and 40 g of ice was added in quick succession. The mixture was stirred for 45 min in a water bath having a temperature of 20°; 10 ml of ethyl acetate and 140 ml of water were then added. The organic phase was extracted five times with 50 ml of water, dried with sodium sulfate, and evaporated at reduced pressure. The residue, which had been freed from all traces of benzene at high vacuum, was dissolved in methanol and its uv spectrum was recorded with a Unicam Sp 800 spectrophotometer. The percentage of $\Delta^{4,7}$-3 ketone in the mixture of $\Delta^{4,7}$- and $\Delta^{4,6}$-3 ketones was then calculated by the equation, % $\Delta^{4,7}$-3 ketone = 100 × wt of $\Delta^{4,7}$-3 ketone/wt of $\Delta^{4,7}$-3 ketone + wt of $\Delta^{4,6}$-3 ketone = $100(A_1\epsilon_1 - 100A_2\epsilon_2)/(A_2\epsilon_3 - A_1\epsilon_1 - A_2\epsilon_2)$, where A_1 = log I_0/I of reaction mixture at 239 mμ, A_2 = fog I_0/I of reaction mixture at 284 mμ, ϵ_1 = 26,500 (284 mμ) for **1** and 28,400 (284 mμ) for **3**, ϵ_2 = 3220 (238 mμ) for **1** and 3745 (238 mμ) for **3**, and ϵ_3 = 16,400 (238 mμ) for **7** and 15,600 (238 mμ) for **9**. The ε value of $\Delta^{4,7}$-3 ketones **7** or **9** at 285 mμ was only 469 or 440, respectively, and was neglected. In the case of 19-hydroxy-4,6-diene **1**, individual runs with cosolvent mixtures containing 0, 20, 40, 60, 80, or 100% of methanol gave products with 86, 86, 80, 73, 33, and 16% $\Delta^{4,7}$-3-one **7**, respectively. In the case of the 10-methyl analog **3**, runs with cosolvent mixtures containing 0, 20, 40, or 60% methanol gave products with 52, 53, 40, and 1% $\Delta^{4,7}$-3-one **9**, respectively.

When the base treatment in the individual runs was prolonged from 5 to 10 min and also when the isomeric mixtures of 4,6-dienes and 4,7-dienes, *i.e.*, of **1** and **7** or of **3** and **9**, was isolated first by thick layer chromatography on silica gel and was then subjected to uv analysis, essentially the same dependencies of the percentage of $\Delta^{4,7}$-3 ketones **3** and **9** on the percentage of methanol in the respective cosolvent mixtures was observed. When the base treatment was further prolonged, by-products were formed in increasing amounts. No formation of $\Delta^{4,7}$-3 ketones could be observed when the base treatment was carried out in 40 ml of methanol instead of the mixture of cosolvent and dimethyl sulfoxide, and starting materials **1** or **3** were recovered largely unchanged.

Androsta-4,7-diene-3,17-dione (9).—When 473 mg of **3** was treated under the conditions outlined above, except that the cosolvent was replaced by dimethyl sulfoxide, a crude product was obtained which, as calculated from its uv spectrum, contained 89% **9**. Chromatography on silica gel yielded a semicrystalline material on elution with benzene–acetone (20:1) which after recrystallization from methanol gave product **9**: mp 129–142°; uv max (EtOH) 238 mμ (ε 15,600); ir ($CHCl_3$) 1736 (17 ketone), 1670 (Δ^4-3 ketone), and 1632 cm^{-1} (>C=C<) nmr 5.82 (s, 1, C-4) and 5.37 ppm (m, 1, C-7).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.44; H, 8.37.

Registry No.—**2**, 29172-45-0; **7**, 2863-83-4; **8**, 29172-47-2; **9**, 4675-73-4; **10**, 29172-49-4; **11**, 29172-50-7; **13**, 29172-51-8; **15**, 29172-52-9; **16**, 29172-53-0.

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Relative Nucleophilicities of Carbanions Derived from α-Substituted Phenylacetonitriles[1]

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The relative nucleophilicities of carbanions derived from α-substituted phenylacetonitriles toward various alkylating agents have been determined in liquid ammonia solution. The nucleophilicities toward methyl iodide are in the order indicated for sodio derivatives of phenylacetonitrile with the following α substituents: ethyl ~ *n*-butyl > methyl > isopropyl > benzyl > hydrogen > 3-pentyl ≫ phenyl. Other data are presented with isopropyl bromide or *n*-butyl halide as alkylating agent and with potassium or lithium as cation. The results are discussed in terms of inductive and steric effects.

The literature contains many examples of the alkylation of phenylacetonitrile with alkyl halides.[3] Of the many bases and solvents employed, the procedure with sodium amide and liquid ammonia is particularly convenient and efficient but gives a product contaminated with the dialkylation product and unreacted phenylacetonitrile.[4]

Mono- and dialkylation occurs as depicted in Scheme I. Studies of the factors in this reaction which would be important in synthesis have been carried out in this laboratory[5] and elsewhere.[6] We now report a quantitative study of the nucleophilicities in liquid ammonia

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(3) A. C. Cope, H. L. Holms, and H. O. House, *Org. React.*, **11**, 107 (1967).

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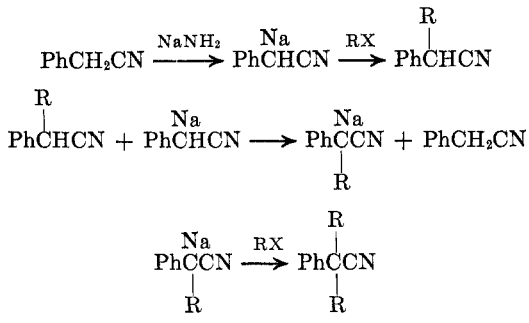
(5) R. L. Bissell, Ph.D. Thesis, Duke University, 1967.

(6) M. Makosza, *Tetrahedron*, **24**, 175 (1968).

SCHEME I

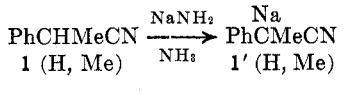


of carbanions derived from α-substituted phenylacetonitriles toward alkyl halides, in which an unusual reactivity series has been found.

In this investigation the *relative* nucleophilicities of such carbanions have been determined by the competitive alkylation of various pairs of carbanions. A quantitative study of relative nucleophilicities by this method must ensure that the initial concentrations of carbanion pairs are accurately known and that the mixtures are homogeneous. The alkylation must be efficient and free of appreciable side reactions. Accurate analyses of alkylation products and residual reactants must be carried out and concentration changes of reactants during alkylation taken into account. All of these conditions have been met in the present study.

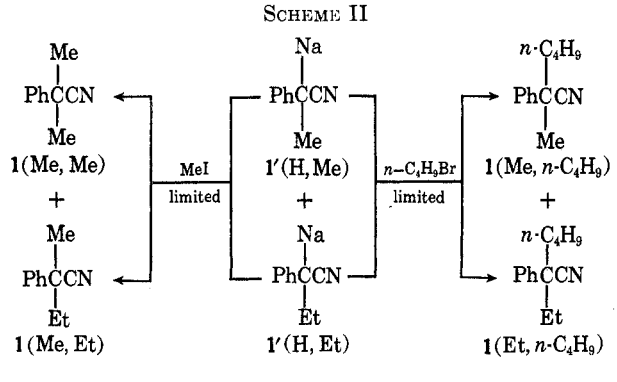
Results

Treatment of an α-substituted phenylacetonitrile **1** with sodium amide in liquid ammonia converts it to the sodionitrile **1′** as shown for the α-methyl derivative. (Throughout this paper a substituted phenylacetonitrile is indicated by the symbol **1** followed by parentheses in which the two α substituents are listed. A prime on **1** designates the derived carbanion.) Relative



nucleophilicities were determined by treating a mixture of two sodionitriles so prepared with a *limited* amount of alkylating agent, to produce alkylation products of the form PhCRR′CN. For example, Scheme II depicts the treatment of an equimolar mixture of **1′**

SCHEME II



(H, Me) and **1′** (H, Et) with a limited amount of *n*-butyl bromide to produce limited amounts of alkylation products **1** (Me, n-C_4H_9) and **1** (Et, n-C_4H_9). The more reactive carbanion [**1′** (H, Et) in this case] gave rise to the greater quantity of its alkylation product, and the relative nucleophilicity of the two carbanions toward *n*-butyl bromide was calculated from the alkylation products ratio, as discussed later. Similarly, treatment of the mixture of carbanions with a limited amount of methyl iodide gave a mixture of **1** (Me, Me) and **1** (Me, Et), and the relative nucleophilicity toward methyl iodide was calculated.

The validity of relative nucleophilicities so determined depends upon the complete conversion of both nitriles to the sodio derivatives before alkylation. While amide ion is clearly a base of sufficient strength to effect the complete conversion,[7] a large excess of amide ion leads to side reactions and a deficiency to very erroneous values for relative nucleophilicities (see Experimental Section). In the present work, the presence of a slight excess of alkali amide in each experiment was ensured by the use of diphenylmethane as an indicator.

Relative nucleophilicities were calculated with the formula in eq 1, in which the parentheses denote con-

$$\text{relative nucleophilicity, nitrile A:nitrile B} = \frac{\left(\begin{smallmatrix}\text{alkylation}\\ \text{product from A}'\end{smallmatrix}\right)}{\left(\begin{smallmatrix}\text{alkylation}\\ \text{product from B}'\end{smallmatrix}\right)} \times \frac{\text{(average B}')}{\text{(average A}')} \quad (1)$$

centrations and the primes indicate the corresponding carbanions. The ratio of concentrations of alkylation products is multiplied by the inverse ratio of average carbanion concentrations during the course of the alkylation, in order to allow for relative concentration changes of the reactant carbanions. The use of the average concentration is considered to be a very good approximation for the effective concentration in this case, inasmuch as carbanion concentration changes were moderate. Final concentrations of starting carbanions were 60–90% of the initial concentrations, and the average concentration was taken to be the mean of the initial and final values. The use of approximate calculations by eq 1 is considered to be more appropriate here than an analytical mathematical treatment, since the value of the first quotient in eq 1 could be determined more accurately than the absolute concentrations of either product (see Experimental Section). The relative nucleophilicities so calculated are concentration adjusted and represent determinations of true relative rates, not limiting values.

Table I records the results of the relative nucleophilicity determinations depicted in Scheme I and of similar experiments using other pairs of carbanions. For a given pair, the initial molar ratio of carbanions was varied from 1 to 3 and that of alkyl halide to total nitrile from 0.12 to 0.45 in various trials. The variations caused no trending in the calculated relative nucleophilicities, giving strong support to the validity of the method. Analyses for total starting material and products were usually 90–100 mol % of the initial totals, indicating that side reactions are unimportant.

The data are internally consistent, as indicated by a comparison of the methylation expt 1, 2, 6, 7, and 8. The relative nucleophilicity value of 1.04 (expt 8)

(7) We estimate the pK of phenylacetonitrile to be about 20 based upon the value of 25 for acetonitrile (see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 12). The value for ammonia is 34–36 (see D. J. Cram, *ibid.*, pp 14, 20; D. C. Ayers, "Carbanions in Synthesis," Oldbourne Press, London, 1966, p 3).

TABLE I

RELATIVE NUCLEOPHILICITIES OF PAIRS OF α-SUBSTITUTED SODIOPHENYLACETONITRILES, $C_6H_5CNaRCN$ (1′), TOWARD ALKYL HALIDES

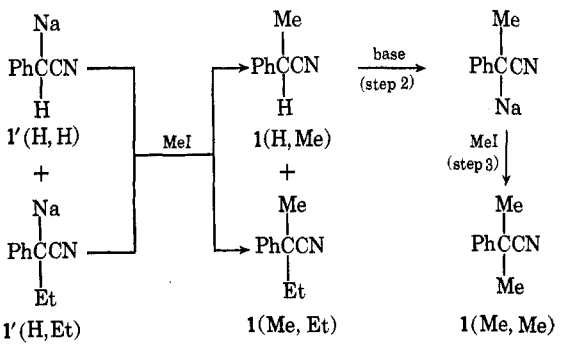
Expt no.	R, in nitrile A	R, in nitrile B	Alkyl halide	Alkylation time, min	Alkylation efficiency,[a] %	No. of trials	Average relative nucleophilicity,[b] A:B
1	Et	H	MeI	10	89–97	4	2.28 ± 0.09
2	n-C_4H_9	H	MeI	10	85–92	3	2.22 ± 0.02
3	$CHMe_2$	H	MeI	10	93–100	3	1.28 ± 0.07
4	$PhCH_2$	H	MeI	10	70–95	3	1.01 ± 0.07
5	$CHEt_2$	H	MeI	10	87–94	2	0.264 ± 0.010
6	Et	Me	MeI	10	65–72	2	1.67 ± 0.06
7	n-C_4H_9	Me	MeI	10	60–71	2	1.64 ± 0.09
8	Et	n-C_4H_9	MeI	10	72–82	2	1.04 ± 0.03
9[c]	$CHEt_2$	Ph	MeI	10	88	1	24.8
10[d]	n-C_4H_9	H	MeI	10	84–86	2	2.70 ± 0.2
11[e]	n-C_4H_9	H	MeI	15	86–87	2	2.42 ± 0.3
12	Et	H	n-C_4H_9Br	20	85–100	3	5.3 ± 0.4
13	Et	H	n-C_4H_9I	10	96–100	2	5.5 ± 0.2
14	Et	H	n-C_4H_9Cl	30–45	20–29	2	4.5 ± 0.1
15	Me	H	n-C_4H_9Br	20	62–70	2	3.2 ± 0.4
16	Et	Me	n-C_4H_9Br	15	82	1	1.57
17	n-C_4H_9	H	Me_2CHBr	30	55–75	2	4.4 ± 0.6
18	$CHEt_2$	H	Me_2CHBr	20–60	10–13	2	0.19 ± 0.04

[a] See Experimental Section. [b] The average deviation is given for each value. [c] Diphenylmethane indicator color was not visible in this case. A 25 mol % excess of $NaNH_2$ was employed. [d] The cation was potassium in this case. [e] The cation was *lithium* in this case.

for 1′ (H, Et):1′ (H, n-C_4H_9) accords within experimental precision with the value 1.03 for the ratio 1′ (H, Et):1′ (H, H)/1′ (H, n-C_4H_9):1′(H, H) (expt 1, 2) and with the value of 1.02 for the ratio 1′ (H, Et):1′ (H, Me)/1′ (H, n-C_4H_9):1′ (H, Me) (expt 6, 7). Similarly, for n-butylation, the 1′ (H, Et):1′ (H, Me) value of 1.57 (expt 16) accords with the value 1.7 for the ratio 1′ (H, Et):1′ (H, H)/1′ (H, Me):1′ (H, H) (expt 12, 15).

Experiments involving sodiophenylacetonitrile, 1′ (H, H), differed from those involving pairs of α-substituted carbanions in that both mono- and dialkylation products were obtained from 1′ (H, H). Also, in such experiments the alkyl halide employed must not have an alkyl group identical with the α substituent of the other nitrile; otherwise, the monoalkylation product of the latter is identical with the dialkylation product of 1 (H, H). For example, Scheme III illustrates the methylation of a mixture of 1′ (H, H) and 1′ (H, Et).

SCHEME III



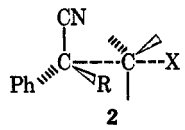
The monoalkylation product 1 (H, Me) is appreciably acidic and underwent ionization as shown by step 2, followed by further reaction with methyl iodide (step 3) to produce 1 (Me, Me). The base involved in step 2 could have been either of the reactant carbanions. A proton transfer reaction of this type would tend to lower the concentration of both carbanions during alkylation to an indeterminant extent; however, the effect would doubtless be greater on the more basic carbanion, probably 1′ (H, Et). The disproportionate lowering of the concentration of 1′ (H, Et) would lead to erroneous values of relative nucleophilicity which would trend toward unity (see eq 1). The lowering would be most pronounced when a relatively large proportion of alkylating agent was taken and when the initial concentration of 1′ (H, H) was large relative to the other carbanion. No trending was observed when such variations of reaction parameters were applied to the given pair of carbanions nor to other similar pairs. It is concluded that the excess amide ion present (see Experimental Section) served as the base in step 2 and that proton transfer reactions among carbanions gave rise to no detectable errors in these experiments. The fact that the second alkylation step (Scheme III, step 3) also consumes alkylating agent has no effect on the validity of the calculations by eq 1, provided the concentration of alkylation products derived from 1′ (H, H) is understood to be the sum of its mono- and dialkylation products.

Discussion

The data of Table I indicate an unusual reactivity series for various 1′ toward methyl iodide. In terms of the α substituents, the nucleophilicities of the sodio derivatives are as follows relative to 1′ (H, H): ethyl, 2.28; n-butyl, 2.22; methyl, 1.37; isopropyl, 1.28; benzyl, 1.01; hydrogen, 1.00; 3-pentyl, 0.26; phenyl, 0.011. Apparently the reaction rate is quite insensitive to the steric bulk of the α substituent. Even with a relatively bulky isopropyl substituent, the carbanion is more reactive than the unsubstituted one. Substitution of the larger 3-pentyl group does decrease the reactivity but not markedly.

The reaction of a carbanion with an alkyl halide is known to proceed by an S_N2 mechanism.[3] The very

slight steric effect observed in the present work is ascribed to the fact that the substituent is at the attacking carbanionic center, rather than at the carbon undergoing substitution, and bends away from the alkyl halide as the transition state is approached and the sp^2 hybrid orbitals at the carbanionic center attain more p character. The transition state is depicted by structure 2. The data indicate further that the inductive



2

effects of alkyl groups are comparable to the steric effects in the present cases, if we assume that solvation effects are negligible. Thus, the slightly greater electron-donating effect of ethyl compared to methyl makes 1′ (H, Et) more reactive than 1′ (H, Me) in spite of the larger size of the former (see expt 6). Although models indicate steric hindrance from isopropyl to be somewhat greater than from benzyl, the data show 1′ (H, $CHMe_2$) to be slightly *more* reactive than 1′ (H, $PhCH_2$). Particularly interesting is the benzyl–butyl comparison (expt 2, 4). In view of the previously discussed steric insensitivity of the reaction and the fact that these two groups differ only beyond the first carbon, the lower reactivity of 1′ (H, $PhCH_2$) may be ascribed mostly to inductive effects; the electron-withdrawing effect of the phenyl group partly counteracts the electron-donating effect of the methylene of the benzyl group. Supporting this conclusion is the ethyl–butyl comparison (expt 1, 2). Despite the disparate steric bulk, the carbanion reactivities are nearly equal because of nearly equal inductive effects.

Although the inductive effects of alkyl groups are discussed here in classical electron-donating terms, the results of some recent theoretical calculations indicate that the *more* branched alkyl groups better stabilize adjacent negative charge in the gas phase.[8] However, as pointed out by Lewis,[8a] such stabilization may not occur in solution where solvated ions are involved.

The general steric insensitivity of the reaction is also illustrated by experiments with *n*-butyl and isopropyl halides (Table I). Toward *n*-butyl bromide, 1′ (H, Et) is 1.57 times more reactive than 1′ (H, Me), in agreement with 1.67 for the less bulky alkylating agent methyl iodide. It is interesting that *n*-butyl bromide is more discriminating than methyl iodide, by a factor of about 2, toward the carbanion pair 1′ (H, Et):1′ (H, H) (*cf.* expt 1, 12) as well as the pair 1′ (H, Me):1′ (H, H) (*cf.* expt 1, 6, 15). Despite its greater bulk, *n*-butyl bromide exhibits a stronger preference for the substituted carbanions than does methyl iodide. The identity of the departing halide has little effect upon selectivity for *n*-butylation (expt 12–14), suggesting that the carbon–halogen bond is largely broken in the transition states.

Isopropyl bromide gives about the same discrimination with the 1′ (H, *n*-C_4H_9):1′ (H, H) pair (expt 17) as does *n*-butyl bromide with the 1′ (H, Et):1′ (H, H) pair. Only when a much bulkier substituent, 3-pentyl, is involved, is an overriding steric effect evident. Thus isopropyl bromide gives relatively less reaction with 1′ (H, $CHEt_2$) (expt 18) than does methyl iodide (expt 5).

As expected, the α-phenyl group caused a large decrease in reactivity (expt 9). Both steric and electronic effects deactivate the carbanion in this case. When the data of expt 5 and 9 are compared, 1′ (H, Ph) is about 100 times less reactive than 1′ (H, H) toward methyl iodide.

When the cation was varied among lithium, sodium, and potassium, the pair 1′ (*n*-C_4H_9, H):1′ (H, H) showed approximately the same relative nucleophilicity toward methyl iodide (expt 2, 10, 11). Since the steric requirements of the cations would be expected to be unimportant, it appears that the relative basicity of the carbanionic pair is insensitive to change in alkali metal cation.

Relatively small differences such as those reported here for variations of the α-alkyl group have also been reported in previous studies of structure *vs.* nucleophilicity for ambident[9] carbanions in solvents such as alcohols and ethers. The comprehensive work of Zook and Rellahan[10] on the rates of alkylation of sodium enolates of alkyl phenyl ketones reports, for example, the rates for ethyl bromide with various α-alkyl derivatives of sodioacetophenone. The relative rates are as follows with the indicated α substituents: unsubstituted, 1.0; methyl, 1.6; ethyl, 1.0; *n*-propyl, 0.9; *n*-butyl, 0.8. Thus, it appears that the steric effects, albeit small, are more important in such enolates than in carbanions from phenylacetonitrile. Small alkyl substituent effects have been recorded for other enolates with regard to nucleophilicity[11] and basicity,[12] and for malonic esters[13] and β-keto esters.[14]

Makosza[6] has reported the competitive alkylation of some pairs of α-substituted phenylacetonitriles with alkyl bromides and sodium amide. The product ratios obtained were discussed in terms of their implications for synthesis. No variation of nitrile or bromide proportions was reported and only one case was treated in which both nitriles were substituted. Although no identical carbanion pair–alkyl halide systems were treated in the present work, in comparable cases the product ratios are in qualitative agreement. Relative nucleophilicity calculations cannot be made with Makosza's data since most of the cases report the analysis of only one reactant and its alkylation products, and since only relative product mixture compositions are reported, rather than absolute analyses. While we are in substantial agreement with Makosza's conclusions with regard to synthesis, it should be mentioned that he has employed concentration levels appropriate for synthesis (approximately 40 times more concentrated than

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TABLE II

PREPARATION OF NEW COMPOUNDS

Compd	Registry no.	Method	Yield, %	Bp, °C (mm) or mp, °C	Formula	Calcd, %			Found, %		
						C	H	N	C	H	N
3-Ethyl-2-phenylvaleramide	29850-91-7	A	67	136–136.5[a]	$C_{13}H_{19}NO$	76.05	9.34	6.82	76.04	9.52	6.55
3-Ethyl-2-phenylvaleronitrile	22101-43-5	A	68[b]	111 (2)	$C_{13}H_{17}N$	83.37	9.15	7.48	83.48	9.38	7.30
2-Methyl-2-phenylbutyronitrile	5558-93-0	B[c]	67	70–72 (0.35)	$C_{11}H_{13}N$	82.97	8.23	8.80	82.99	8.24	8.73
2,3-Diphenyl-2-methylpropionitrile	5558-92-9	B[c]	71	165–170 (1)[d]	$C_{16}H_{15}N$	86.84	6.83	6.33	86.99	7.04	6.07
2,3-Dimethyl-2-phenylbutyronitrile	29936-67-2	C[c]	40	84 (1.5)	$C_{12}H_{15}N$	83.19	8.73	8.08	82.94	8.70	8.35
3-Ethyl-2-methyl-2-phenylvaleronitrile	29850-95-1	C[c,e]	66	91–92 (0.7)	$V_{14}H_{19}N$	83.53	9.51	6.96	83.29	9.62	7.08
2-Isopropyl-2-phenylhexanenitrile	29850-96-2	C[e,f]	76	96–96.5 (0.8)	$C_{15}H_{21}N$	83.66	9.83	6.50	83.90	10.09	6.57
3-Ethyl-2-isopropyl-2-phenylvaleronitrile	29850-97-3	C[f]	57[g]	89.5–91 (0.2)	$C_{16}H_{23}N$	83.78	10.11	6.11	83.51	10.26	6.26

[a] Crystallized from benzene. [b] Based on the carboxamide. [c] With MeI. [d] Mp 40.5–42.5° when distillate crystallized. [e] Twice the stoichiometric amounts of $NaNH_2$ and alkyl halide were used. [f] With Me_2CHBr. [g] The crude product contained 20% starting material.

ours) and has not ruled out the possibility of partial solubility.

Experimental Section[15]

Preparation of Mono- and Dialkylphenylacetonitriles.—2-Phenylpropionitrile, 2,3-diphenylpropionitrile, 2-phenylhexanenitrile, and 2-*n*-butyl-2-phenylhexanenitrile were prepared as previously described.[4] Other compounds were prepared by one of the three general methods described below. Reaction mixtures were worked up by neutralizing with 10% HCl, extracting with ether, drying and concentrating the extracts, and distilling or crystallizing the residue. The properties of compounds which appear to be new are given in Table II and those of other compounds in Table III. The starting nitriles used in this work had purity greater than 99.5% by vpc. Dialkylphenylacetonitriles for calibration mixtures had purity greater than 99% by vpc.

Method A.—According to the indirect route of Kaiser and Hauser,[16] α-alkylphenylacetamides were prepared by alkylation of disodiophenylacetamide and dehydrated to the corresponding nitrile with *n*-butyllithium.

Method B.[4]—Monoalkylphenylacetonitriles were alkylated with excess NaH and excess alkyl halide.

Method C.—A monoalkylphenylacetonitrile was stirred 30 min with 4 equiv of $NaNH_2$ in liquid NH_3. Alkyl halide, 4 equiv, was added dropwise over 5–10 min, and the mixture stirred 15–60 min and quenched with NH_4Cl. Dialkylphenylacetonitriles in which the alkyl groups were identical were prepared in one step from phenylacetonitrile by the same procedure.

Relative Nucleophilicity Experiments.—The most critical factor was the quantity of sodium amide taken. Use of less than the stoichiometric amount led to incomplete generation of the more basic (and probably more nucleophilic) carbanion and erroneous alkylation product ratios. While a moderate excess (~20 mol %) of sodium amide did not appear to be harmful, a large excess led to a reduced alkylation efficiency[17] and nonreproducible alkylation product ratios. Accurate determination of the quantity of alkali metal amide taken is difficult experimentally, especially with small quantities. Commercial samples are of questionable purity and generation of the material from the metal *in situ* may be incomplete and subject to side reactions. In the present work the use of diphenylmethane as an indicator served as a rapid, convenient procedure to adjust the concentration of alkali metal amide.

The two nitriles were added to excess alkali metal amide in liquid NH_3 and a small amount (*ca.* 2 mol % of total nitriles) of diphenylmethane was then added to produce the orange diphenylmethide ion. Sodionitrile mixtures made with commercial sodium amide were faintly green and clearly homogeneous. The indicator color was readily visible. When sodium amide generated *in situ* was used, the mixtures obtained were dark colored and opaque, masking the indicator color. Hence a commercial product (Fisher Scientific Co.) was employed for trials with sodium cation. When lithium or potassium amide generated *in situ* was used to form the nitrile carbanions, the indicator color change could be observed satisfactorily. The excess amide ion was neutralized by the addition in small portions of solid NH_4Cl to discharge the orange color (*vide infra*). A moderate amount of sodium amide (10–30 mol % of total nitriles) remains after discharge of the orange color, as shown by control experiments in which an excess of alkyl halide was added to **1′** (H, H). An average of more than one alkyl group per molecule was incorporated [see discussion of dialkylation of **1** (H, H)].

In a typical experiment, 350 ml of anhydrous NH_3 was distilled into a flask equipped with a dewar condenser and mechanical stirrer. The flask was blanketed with N_2, and 50 mmol of commercial $NaNH_2$, weighed under N_2, was introduced into the flask followed by a mixture of two nitriles, totaling *ca.* 12 mmol, in 20 ml of ether.[18] The mixture was stirred for 15 min to give a

(15) Melting points and boiling points are uncorrected. Nmr spectra were determined at 60 MHz on a Varian A-60 spectrometer. Vpc analyses were performed on an F & M Model 700 chromatograph with thermal conductivity detector and mechanical integrator using a 0.25 in. × 20 ft column packed with 20% SE-30 silicone gum rubber. Ethyl ether was distilled from $LiAlH_4$. Alkyl halides were dried and distilled.

(16) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **35**, 3873 (1966).

(17) Alkylation efficiency is used here to mean the fraction of moles of alkylation agent incorporated into nitriles as new alkyl groups.

(18) **1** (H, $PhCH_2$), which is not very soluble in ether, was introduced in solid form.

TABLE III
PREPARATION OF KNOWN COMPOUNDS

Compd	Registry no.	Method	Yield, %	Bp, °C (mm), or mp, °C	Lit. bp, °C (mm), or mp, °C
2-Phenylbutyramide	90-26-6	A	93	73–74	75–77[a]
3-Methyl-2-phenylbutyramide	5470-47-3	A	48	108–110	99–101[b]
2-Phenylbutyronitrile	769-68-6	A	38[c]	102–103 (7)	128 (16)[d]
3-Methyl-2-phenylbutyronitrile	5558-29-2	A	52[c,e]	73–74.5 (0.6)	110 (7)[f]
2-Ethyl-2-phenylhexanenitrile	5558-55-4	B[g]	28	100–105 (0.8)	112–115 (2)[b]
2-Methyl-2-phenylpropionitrile	1195-98-8	C[h]	58[i]	79 (2.5)	100–103 (12)[j]
2,2-Diphenylpropionitrile	5558-67-8	C[k]	60	135 (0.7)	141 (1.5)[f]
2-Isopropyl-3-methyl-2-phenylbutyronitrile	29936-68-3	C[l]	90	93.5 (1.2)	174.4–174.5 (49)[m]
2-Methyl-2-phenylhexanenitrile	4355-47-9	C[n]	56	93–95 (1)	114–115 (4)[b]

[a] N. Bikova and L. Zhelyazkov, *Tr. Nauch.-Issled. Inst. Farm.*, **3**, 29 (1961); *Chem. Abstr.*, **61**, 6948*f* (1964). [b] G. Vasiliu and F. Cocu, *Rev. Chim. (Bucharest)*, **18**, 259 (1967); *Chem. Abstr.*, **67**, 108408m (1967). [c] Based on the carboxamide. [d] D. Zavoianu and F. Cocu, *Rev. Chim. (Bucharest)*, **18**, 2 (1967); *Chem. Abstr.*, **67**, 32438y (1967). [e] Preparation from phenylcyanoacetic acid (ref 13) gave <10% yield. [f] M. Makosza and B. Serafin, *Rocz. Chem.*, **39**, 1401 (1965). [g] With n-C_4H_9Br. [h] Mixture of 4 equiv of MeI and 1 equiv of $PhCH_2CN$ added to 4 equiv of $NaNH_2$ in ammonia. [i] Yield 51% by method B. [j] J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958). [k] With MeI. [l] With Me_2CHBr and $PhCH_2CN$. [m] D. J. Cram, F. Elhafez, and H. L. Nyquist, *J. Amer. Chem. Soc.*, **76**, 22 (1954). [n] With n-C_4H_9Br using stoichiometric ratio of reactants.

transparent, light green solution. Diphenylmethane, 1–2 drops, was added and a bright orange color appeared at once. Solid NH_4Cl was added in small portions until the orange color was discharged and the green had reappeared. The bright orange color quickly returned and was again discharged in the same manner. The process was repeated four to six times over a period of 20 min until *ca.* 2 mg was sufficient to discharge the orange color and a green or green-orange color persisted for at least 2 min.[19] The alkyl halide in 20 ml of ether was added dropwise with vigorous stirring over a period of 3 min from a dropping funnel blanketed with N_2. The mixture was stirred for the time period indicated in Table I and neutalized with excess NH_4Cl. Ether was added and the NH_3 was allowed to evaporate. The mixture was neutalized with 10% HCl and extracted three times with 100-ml portions of ether. The combined extracts were dried and carefully concentrated *in vacuo* so as not to selectively remove volatile products. To the residue, which contained 50–80% ether, was added the internal standard and the resultant clear solution was analyzed by vpc. A control run without alkylation gave a total nitrile analysis which was 95 mol % of the initial total. An appropriate internal standard was chosen for each experiment to give a vpc peak which fell among the product peaks but was well resolved from them.

All carbanion mixtures were homogeneous. The alkyl halide in ether dissolved immediately upon addition to the NH_3 solution. The rate of mixing of the alkyl halide was faster than the rate of alkylation, even for methyl iodide. If mixing were relatively slow, the product ratio would mirror the ratio of the local concentrations of reactant carbanions.

Vpc Analysis.—Reaction mixtures were chromatographed under isothermal conditions.[20] Every component was eluted. Components were well resolved, with at least a 60% valley between adjacent peaks in the least favorable case. A calibration mixture, with approximately the same composition of nitriles, internal standard, and ether as the reaction mixture, was prepared from pure, authentic compounds and chromatographed immediately following the reaction mixture under identical conditions. Peak areas were related to molar composition by the use of relative response factors,[21] which agreed within 2% relative from day to day. The total analysis of each nitrile with its alkylation products typically exceeded 90 mol % of the initial quantity. A second chromatogram was obtained with a larger sample injection in order to maximize the peak heights of the alkylation products. The calibration mixture was similarly rechromatographed. More precise values of concentrations of alkylation products for eq 1 were obtained from the second chromatogram. Final concentrations of reactant carbanions were obtained from the first chromatogram. Initial carbanion concentrations were calculated from weight data. The average reactant carbanion concentrations for eq 1 were taken to be the mean of the initial and final values.

Nmr Spectra.—Unless otherwise noted, spectra were taken in $CDCl_3$ with respect to internal TMS. All spectra for compounds in Tables II and III accord with assigned structures and are as follows. **3-Ethyl-2-phenylvaleramide**: DMSO-d_6 δ 7.27 (m, 5), 3.42 (d, 1, J = 10.5 Hz, $PhCH_2$), 1.75-1.20 (m, 4, CH_2), 0.90 (t, 3, J = 7 Hz, Me), 0.78 (t, 3, J = 7 Hz, Me). **3-Ethyl-2-phenylvaleronitrile**: δ 7.39 (s, 5), 3.89 (d, 1, J = 5 Hz, PhCH), 1.8–1.1 (m, 5, $CHEt_2$, CH_2Me), 0.93 (t, 6, J = 6 Hz, Me). **2-Methyl-2-phenylbutyronitrile**: CCl_4 δ 7.25 (m, 5), 1.90 (quartet, 2, J = 7 Hz, CH_2), 1.63 (s, 3, PhCMe), 0.93 (t, 3, J = 7 Hz, CH_2Me). **2,3-Diphenyl-2-methylpropionitrile**: CCl_4 δ 7.21 (s, 5), 7.06 (m, 5), 3.00 (s, 2, CH_2), 1.62 (s, 3, Me). **2,3-Dimethyl-2-phenylbutyronitrile**: CCl_4 δ 7.29 (m, 5), 1.95 (m, 1, CH), 1.65 (s, 3, PhCMe), 1.13, 0.82 (d, 3, J = 6.5 Hz, $CHMe_2$). **3-Ethyl-2-methyl-2-phenylvaleronitrile**: δ 7.6–7.1 (m, 5), 1.68 (s, 3, PhCMe), 1.8–0.6 (m, 11, $CHEt_2$). **2-Isopropyl-2-phenylhexanenitrile**: δ 7.33 (s, 5), 2.5–1.7 (m, 3, $CHMe_2$, $CH_2C_3H_7$), 1.19, 0.77 (d, 3, J = 7 Hz, $CHMe_2$). **3-Ethyl-2-isopropyl-2-phenylvaleronitrile**: δ 7.36 (s, 5), 2.53 (septet, 1, J = 7 Hz, Me_2CH), 2.1–1.2 [m, 5, $CH(CH_2Me)_2$], 1.2–0.6 (m, 12, Me_4). **2-Phenylbutyramide**: δ 7.29 (s, 5), 6.1 (m, 2, NH_2), 3.30 (t, 1, J = 7.5 Hz, CH), 1.9 (m, 2, CH_2), 0.86 (t, 3, J = 7.5 Hz, Me). **3-Methyl-2-phenylbutyramide**: δ 7.23 (s, 5), 5.9 (m, 2, NH_2), 2.96 (d, 1, J = 10 Hz, PhCH), *ca.* 2.3 (m, 1, Me_2CH), 1.05, 0.69 (d, 3, J = 6 Hz, Me_2). **2-Phenylbutyronitrile**: CCl_4 δ 7.21 (s, 5), 3.63 (t, 1, J = 7 Hz, CH), 1.85 (m, 2, J = 7 Hz, CH_2), 1.02 (t, 3, J = 7 Hz, Me). **3-Methyl-2-phenylbutyronitrile**: CCl_4 δ 7.30 (s, 5), 3.64 (d, 1, J = 6 Hz, PhCH), 2.02 (m, 1, J = 6.5 Hz, $CHMe_2$), 1.03, 0.99 (d, 3, J = 6.5 Hz, $CHMe_2$). **2-Ethyl-2-phenylhexanenitrile**: δ 7.39 (s, 5), 1.91 (m, 4, J = 7 Hz, CH_2Me and $CH_2C_3H_7$), 1.6–0.5 (m, 10, CH_2Me, $CH_2C_3H_7$). **2,2-Diphenylpropionitrile**: CCl_4 δ 7.23 (s, 10), 2.00 (s, 3, Me). **2-Isopropyl-3-methyl-2-phenylbutyronitrile**: δ 7.33 (s, 5), 2.48 (septet, 2, J = 6.5 Hz, $CHMe_2$), 1.01, 0.87 (d, 3, J = 6.5 Hz, $CHMe_2$).

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(19) The slowness with which the mixture comes to equilibrium probably explains the presence of excess amide ion mentioned previously. With potassium as cation, the color change was fast and permanent. With lithium, the change was very slow and the neutralization process required *ca.* 2 hr.

(20) Mixtures containing components with widely disparate volatilities were chromatographed with a "step" program, in which the initial constant temperature was quickly raised, between components, to a final constant value at which the less volatile components were all eluted.

(21) See S. Dal Nogare and R. S. Juvet, Jr., "Gas–Liquid Chromatography," Interscience, New York, N. Y., 1962, p 197.