°C dec. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: c, 51.74; H, 4.56; N, 6.03. Found: C, 51.66; H, 4.66; N, 6.03.

Potassium Borohydride Reductions. General Procedure. A stirred suspension of the quaternary salt (3 mmol) in a mixture of ethanol (24 ml) and water (11 ml) was heated to reflux. Potassium borohydride (36 mmol) was added in small aliquots over a period of 30 min. Refluxing was continued for 4.5 h and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, water (50 ml) was added to the residue, and extraction with ether (3 × 40 ml) followed. The combined organic layers were successively washed with 10% HCl (2 × 25 ml), water (25 ml), 10% NaOH (2 × 25 ml), and water (2 × 25 ml). After drying over Na_2SO_4 the solvent was removed in vacuo to give the toluene derivative (reduction and fragmentation). The combined acid layers were made basic by addition of solid potassium hydroxide under stirring and cooling in ice. Extraction with ether (2 × 25 ml) followed. The organic phases were washed with water and dried and the solvent was removed to yield the N-substituted 1,2,3,4-tetrahydroisoquinoline derivative (reduction and fragmentation), or the substituted 1-benzyl-1,2,3,4-tetrahydroisoquinoline (reduction only).

A. Reduction of 1-(4-Methoxy-2-nitrobenzyl)isoquinoline Propiodide (1c). Under identical conditions as described above 1.4 g (3 mmol) of **1c** was reduced to give 0.35 g (69%) of 4-methoxy-2-nitrotoluene (**4a**) and 0.46 g (87%) of 2-propyl-1,2,3,4-tetrahydroisoquinoline (**3b**) as an oil.

The hydrochloride of **3b** was formed and recrystallized from methanol–ether, mp 242 °C (lit.[6] mp 242 °C).

B. Reduction of 1-(2-Methoxy-6-nitrobenzyl)isoquinoline Propiodide (1h). Similarly reduced with 2.0 g (37 mmol) of potassium borohydride was 1.3 g (2.8 mmol) of **1h** to give 0.37 g (79%) of 2-methyl-3-nitroanisole (**4b**), mp 46–49 °C (lit.[7] mp 52 °C), and 0.41 g (84%) of **3b**, which was identified as described above.

C. Reduction of 1-(4-Methoxy-3-nitrobenzyl)isoquinoline Propiodide (1d). Only one product, 1-(4-methoxy-3-nitro)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**5**), was obtained from the reduction of **1d** (2.8 mmol) with 2.0 g (37 mmol) of potassium borohydride. The reaction yielded 0.75 g (79%) of **5** as an oil.

A hydriodide of **5** was prepared, mp 184–185 °C. Recrystallization from absolute ethanol gave an analytical sample, mp 184 °C.

Anal. Calcd for $C_{20}H_{25}IN_2O_3$: C, 51.28; H, 5.38; N, 5.98. Found: C, 51.20; H, 5.45; N, 5.84.

D. Reduction of 1-(4-Nitrobenzyl)isoquinoline Methiodide (1b). Reaction of **1b** (1.3 g, 3.2 mmol) with 2.44 g (45 mmol) of potassium borohydride afforded 0.16 g (36%) of 4-nitrotoluene (**4c**), mp 49–51 °C (lit.[8] mp 54°C), and 0.4 g (85%) of 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**), picrate mp 152–153 °C dec (lit.[5] mp 156 °C dec).

Acknowledgments. We wish to acknowledge the financial support of the state of New Jersey, Department of Health, Division of Narcotic and Drug Abuse Control, and the American Foundation for Pharmaceutical Education for the 1975–1976 Gustaves A. Pfeiffer Memorial Research Fellowship to J.L.N.

Registry No.—**1b,** 60967-77-3; **1c,** 57559-56-5; **1d,** 60967-78-4; **1h,** 60967-79-5; **3a** picrate, 15032-31-2; **3b,** 57928-05-9; **3b** HCl, 57464-74-1; **4a,** 17484-36-5; **4b,** 4837-88-1; **4c,** 99-99-0; **5,** 60967-80-8; **5** HI, 60996-52-3; 1-(4-nitrobenzyl)isoquinoline, 21965-90-2; methyl iodide, 74-88-4; 1-(4-methoxy-3-nitrobenzyl)isoquinoline, 60967-81-9; 1-(2-methoxy-6-nitrobenzyl)isoquinoline, 60967-82-0; iodopropane, 107-08-4.

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Hydrogen Abstraction from Substituted Phenylacetonitriles[1]

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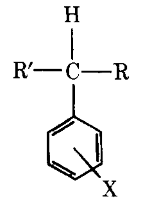
In the course of the development of linear free energy relationships, certain reaction types have required the introduction of new substituent parameters. Hammett's σ^- [3] and Brown's σ^+ [4] values recognize the possible extra stabilization shown by certain functional groups when charge is formed in direct conjugation with the ring. Reactions leading to the formation of benzylic radicals have long been correlated with σ^+ parameters. [5] It also seems likely that benzylic hydrogen abstraction by "nucleophilic radicals" may ultimately yield optimum correlation with σ^-.[6] The generally accepted view is that this would be indicative of charge separation in the transition state of the rate-determining step.[7]

Although there is substantially less documentation, it has been observed that some ring substituents show an enhanced ability to favor certain radical reactions. The copolymerization of substituted styrenes with maleic anhydride, for example, is generally favored by electron-donating groups in the former.[8] The *p*-CN compound, however, exhibits a reactivity which seems far greater than expected. This substituent may also behave anomalously in other systems. Pryor, Davis, and Gleaton have noted that both benzonitrile and nitrobenzene show enhanced reactivity in the para position during radical methylation.[9] This was attributed to an "extra resonance effect". Along these lines, a particularly striking result is the recent observation of Kaba and Ingold that tricyanomethyl radical is an extremely stable species.[10] This must be at least partially attributable to resonance effects and is somewhat surprising as most of the "persistent" carbon radicals studied by Ingold's group show much greater steric congestion at the radical site.[11]

Recently, one of us put forward an empirical approach for the evaluation of Hammett ρ values for benzylic hydrogen abstraction from ring-substituted–α-substituted toluenes, A, by the trichloromethyl radical.[12] The essence of the argument is that for any single series of compounds, the sensitivity toward change of ring substituent would be a function of both the electronic and steric parameters associated with groups directly bonded to the reaction site. This may be expressed by eq 1, where the steric and electronic substituent parameters utilized refer to those for R and R′. Further studies with un-

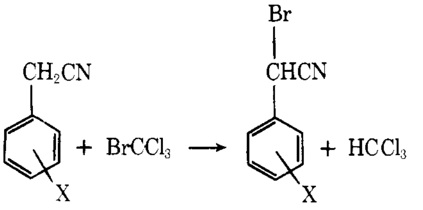


A

tested systems have led to experimental ρ values in excellent agreement with their predicted counterparts.[12,13]

$$\rho = -0.606(\sum \sigma_p^+) + 0.195(\sum E_s) - 1.063 \quad (1)$$

It was felt that the above approach might be utilized to assess the importance and extent of radical stabilizing ability of the cyano group. With this in mind, a series of substituted phenylacetonitriles, B, was prepared and reacted photolytically with bromotrichloromethane at 70 °C (eq 2). The substituted phenylacetonitriles utilized were either purchased or prepared from the corresponding benzyl chlorides by refluxing in aqueous sodium cyanide solution.[14]


B

(2)

Product studies on unsubstituted phenylacetonitrile showed the major product to be the α-brominated compound. Some dibromination also seemed to occur (ca. 12%). Much more surprising was the isolation of relatively large amounts (ca. 23%) of 2,3-diphenylsuccinonitrile. This compound has been prepared by the action of copper powder or sodium iodide on α-bromophenylacetonitrile.[15] Such agents were absent during the present studies, however, and the simplest explanation for the formation of 2,3-diphenylsuccinonitrile is that it arises by coupling of two α-cyanobenzyl radicals. Little, if any, bibenzyl has been observed in the corresponding reaction of toluene. The α-cyano group appears to impart an added stability to the benzylic radical.

Relative rates of reaction were determined as follows. A substituted phenylacetonitrile and the parent compound were made to compete directly for the trichloromethyl radical. Small amounts of chlorobenzene or o-dichlorobenzene were present to function as unreactive internal standard and the reaction course was monitored by GLC. All kinetic runs were carried out in replicate under a nitrogen atmosphere at reduced pressure. Reaction times varied from 91 to 144 h. Total reactivity of the phenylacetonitriles was from 33.7 to 89.9%. The case of p-methylphenylacetonitrile caused an additional problem because of the presence of two nonequivalent benzylic positions. It was found that this compound underwent reaction at the methylene group to an extent of 85.4 ± 0.7%. Relative rates of reaction are given in Table I.

Optimum correlation within the framework of the Hammett equation was with σ^+ parameters. This is not surprising. Almost all hydrogen abstractions using bromotrichloromethane have shown this effect.[5] An experimental ρ value of -0.55 ± 0.02 was obtained. The correlation constant of -0.994 was associated with this value. This result is graphically shown in Figure 1.

A problem arose in calculating the predicted ρ value from eq 1. The Taft steric parameter E_s for the cyano group had apparently not been determined. Qualitatively it was felt that a relatively small linear substituent should have rather modest steric demands. Support for this view can be obtained from the study of group conformational free energy differences in monosubstituted cyclohexanes.[16] On a semiquantitative scale this term for the cyano group is almost negligible. The conformational preference for the cyano group to occupy an equatorial site is even less than that of small single atoms such as fluorine. With this as a guide, a rather large range of possible E_s values was considered between the extremes of cyano equivalent to hydrogen (1.24) and cyano intermediate between hydrogen and methyl (0.62). Utilization of these values in eq 1 (along with an E_s value of 1.24 for hydrogen and the standard electronic parameters[17]) led to calculated ρ values in the range of -0.98 to -1.10.

Table I. Relative Rates of Hydrogen Abstraction from Substituted Phenylacetonitriles by Trichloromethyl Radical at 70 °C

Registry no.	Substituent	σ^+	Rel rate	No. of runs
4693-91-8	p-OCH_3	−0.778	2.82 ± 0.05	5
35675-44-6	p-CH_3[a]	−0.311	1.33 ± 0.05	6
3288-99-1	p-$C(CH_3)_3$	−0.256	1.26 ± 0.08	7
140-29-4	H	0.000	1.00	
140-53-4	p-Cl	0.114	0.81 ± 0.02	7
501-00-8	m-F	0.352	0.64 ± 0.01	6
1529-41-5	m-Cl	0.399	0.60 ± 0.03	5
2338-76-3	m-CF_3	0.520	0.52 ± 0.02	7

[a] Corrected for reaction at the methylene position only.

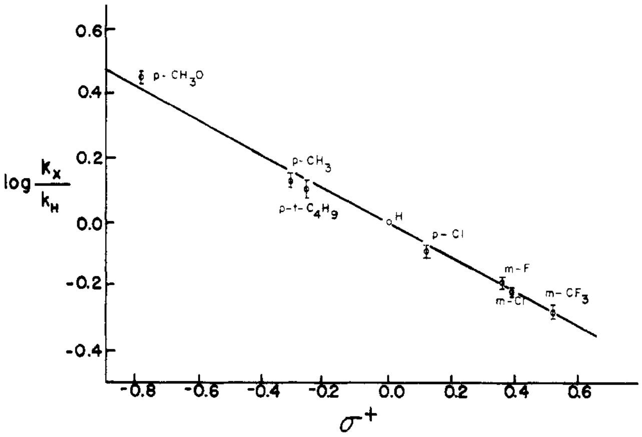


Figure 1. Logarithms of relative rates of reaction vs. σ^+ parameters.

It is felt that the lack of agreement between the experimental and theoretical ρ values is explicable by those special radical stabilizing effects of the cyano group invoked by earlier workers. Before terminating this discussion, however, it should be mentioned that a cyano group bonded directly to the site of a benzylic hydrogen apparently need not always exhibit enhanced resonance stabilization.

Friedrich, Friedrich, Andrews, and Keefer have described the reaction between N-bromosuccinimide and a series of α-substituted toluenes.[18] No particular rate enhancement was observed for the cyano group relative to the other nine substituents examined. The data defined a good linear relationship with σ^+,[18] or with an expanded four-parameter equation which included steric parameters.[19] It is felt, however, that there may be no incongruity between these findings and those reported above.

The enhanced stabilizing effect of the cyano group in hydrogen abstraction reactions should only be observed in extremely endothermic processes wherein the transition state shows pronounced radical character. If different abstracting species are generated from N-bromosuccinimide and bromotrichloromethane,[20] it seems plausible that the latter may be involved in a more endothermic reaction.[19,20] In support of this view, the reactivity of phenylacetonitrile toward bromotrichloromethane is found to be 0.94 ± 0.04 times that of toluene. The ratio of labilities of the respective benzylic hydrogens is 1.41:1 as compared with 0.22:1 found in the reaction with N-bromosuccinimide.[18]

Experimental Section

Materials. All commercial compounds were distilled prior to use. Physical constants agreed with literature values and GLC analysis indicated minimal purities of 99%. Most of the substituted phenylacetonitriles were prepared similarly to the following example. Purities were comparable to those of the other compounds. Physical properties and IR and NMR spectra were in accord with literature values and/or expectation.

Preparation of (*p*-Methylphenyl)acetonitrile. (*p*-Methylphenyl)acetonitrile was prepared by the addition over 35 min of 50 g (0.43 mol) of *p*-methylbenzyl chloride in 50 g of ethanol to 25 g (0.51 mol) of sodium cyanide dissolved in 23 ml of distilled water. The mixture was refluxed at 82 °C with a water-cooled, glass helices packed condenser for 4 h, after which time the mixture had resolved into a dark-brown upper layer and a dark-amber lower layer. The mixture was cooled and suction filtered to remove the precipitated salt, and approximately 60 ml of ethanol was carefully distilled off at 77 °C. The remaining material was extracted with four times its volume of ethyl ether. The organic material was washed with equal volumes of sulfuric acid, saturated sodium bicarbonate, and concentrated sodium chloride solutions, and dried over a few grams of anhydrous magnesium sulfate. After filtration, the material was fractionally distilled. A yield of 5.5 g (13%) of 99.9% pure product was obtained.

Procedure for Kinetic Runs for the Reaction of Bromotrichloromethane with the Substituted Phenylacetonitriles. Solutions of the two phenylacetonitriles, bromotrichloromethane, and *o*-dichlorobenzene (or chlorobenzene) were prepared in the approximate molar ratio of 1:1:10:0.5. Approximately 0.75 ml of the solution was placed in each of the several ampules (usually eight ampules were prepared simultaneously). The ampules were cooled to dry ice–isopropyl alcohol temperature until the solutions solidified. The ampules were evacuated at 0.4–1.5 Torr, filled with nitrogen gas, and then warmed to room temperature. This process was repeated three times. After cooling and evacuation, the tubes were sealed and one was reserved for the analysis of the unreacted starting materials. The remainder were placed horizontally just below the surface of a mineral oil constant temperature bath maintained at 70.0 ± 0.5 °C. The samples were irradiated with ultraviolet light provided by a Sylvania 275-W sun lamp placed 20 cm above the surface of the oil. Reaction times varied from 91.25 to 144.25 h, by which time 33.74–89.89% of the phenylacetonitriles had reacted. The ampules were then cooled and opened. Analysis of the mixtures, both before and after reaction, was carried out via GLC on either a 3% SE-30 on Varaport 30 or a 12% Carbowax 20M on Chromosorb P column. Conversion of raw data to relative rate expressions followed standard techniques.[20]

Registry No.—Bromotrichloromethane, 75-62-7.

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The Facile Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamines

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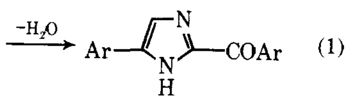
Semiionic compounds such as sulfoxides[1a,b] and amine *N*-oxides[1b–d] have been used to oxidize α-halocarbonyl compounds to α-dicarbonyl compounds. It has been shown recently that the reaction of phenacyl bromides (**1**) with 1,1-dimethylhydrazine resulted in the formation of arylglyoxaldimines (**3**) which then underwent further reactions.[2] Inasmuch as the net result of this reaction amounts to the conversion of the $-CH_2Br$ group to the $-CH{=}NH$ function, it was reasonable to anticipate that *N,N*-dialkylhydroxylamines might convert phenacyl bromides to the corresponding glyoxals. This note describes the results of our investigations of the reaction of phenacyl bromides with *N,N*-diethyl- and *N,N*-dibenzylhydroxylamines.

$$\underset{\mathbf{1}}{ArCOCH_2Br} + \underset{\mathbf{2}}{Me_2NNH_2} \xrightarrow[-HBr]{-Me_2NH} \underset{\mathbf{3}}{[ArCOCH{=}NH]}$$



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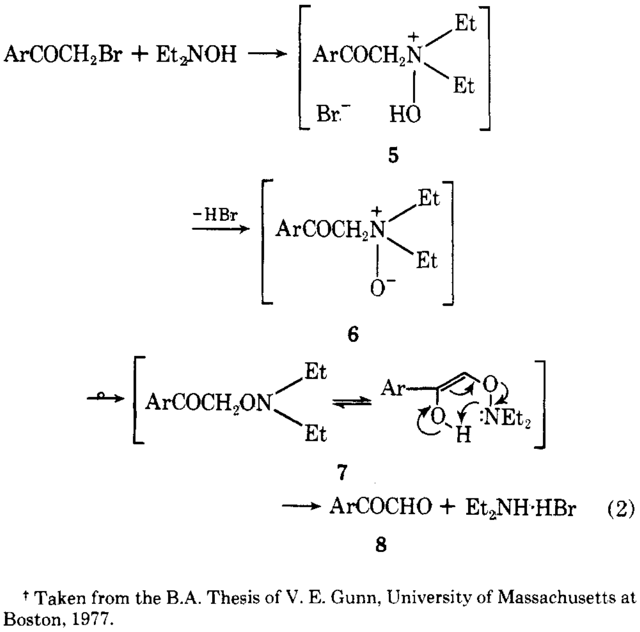
The reaction of phenacyl bromide with *N,N*-diethylhydroxylamine (DEHO) in methanol gave a 78% yield of phenylglyoxal as a thick, yellow-orange oil which slowly hydrated on standing, mp 90–91 °C, identical with an authentic sample.[3] Similarly, other phenacyl bromides were converted to the corresponding glyoxals in good to excellent yields (Table I), although no attempts were made to optimize the yields.

To our knowledge, this is the first report of the use of *N,N*-dialkylhydroxylamines as *oxidizing* agents for organic compounds,[4] which is to be contrasted with the recent disclosure of the *reduction* of *p*-benzoquinones to the corresponding hydroquinones with *N,N*-diethylhydroxylamine.[5] By analogy with the reaction of 1 with *N,N*-dimethylhydra-



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† Taken from the B.A. Thesis of V. E. Gunn, University of Massachusetts at Boston, 1977.