in the summation not present in the constituent parts. Such intramolecular interactions which we have so far observed are electronic, hydrogen bonding, and the shielding effects considered in this report. The shielding may be of two kinds. For example, when two apolar groups are adjacent (*e.g.*, *ortho*) to each other, they will not have the same number of structured water molecules around them as when separated (*e.g.*, *para*). The other type of shielding occurs from folding in nonrigid molecules. In this type one can expect an important role for intramolecular hydrophobic bonding.

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The Reaction of Some Quaternary Hydrazones with Grignard Reagents[1]

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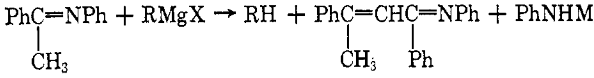
Quaternary hydrazones of the type $Ar_2C{=}NN^+R_3I^-$ were prepared by treating various benzophenone dialkylhydrazones with methyl iodide. They reacted exothermically with Grignard reagents to form substances from which the quaternary hydrazone could be recovered on mild hydrolysis. Upon refluxing in tetrahydrofuran, further reaction took place, involving N–N cleavage, leading to tertiary amine, benzophenonimine, N-substituted benzophenonimine, and biaryl (or bialkyl) (eq 3 and 4). A small part of the N-substituted imines corresponded to C to N migration of a C-aryl group, to account for which an amine N-imide intermediate is proposed (eq 5). However, the ratios of the N-attached groups from experiments in which the group in the Grignard reagent and those on the azomethine carbon were different are not consistent with known migration aptitudes and indicate that the major proportion of N-substituted imine arises by direct substitution on the nitrogen. *p*-Chlorobenzaldehyde quaternary hydrazone reacted with *p*-tolylmagnesium bromide to give *p*-methyl-*p*′-chlorobenzophenonimine, which may have arisen through initial base-catalyzed elimination to *p*-chlorobenzonitrile.

It is well known[2] that the azomethine system is less reactive than the carbonyl system toward addition of organometallic reagents, a consequence presumably of greater electronic symmetry. Although aldimines undergo conventional addition of Grignard reagents more or less readily, ketimines may undergo a competing base-catalyzed aldol-type condensation instead,[3] even to the complete exclusion of addition. In such cases, the ketimine acts as a source of active hydrogen and destroys the Grignard reagent (eq 1). Benzophenone anil reacts exothermically with phenylmagnesium bromide to form a complex, from which the anil may be recovered unchanged by hydrolysis.[3] When forcing conditions are used, 1,4 addition occurs, giving N-*o*-phenylbenzhydrylaniline.[4] Phenyllithium, however, adds conventionally to give N-triphenylmethylaniline.[5]



$$\underset{\mathrm{CH_3}}{\mathrm{PhC}}{=}\mathrm{NPh} + \mathrm{RMgX} \rightarrow \mathrm{RH} + \mathrm{Ph}\underset{\mathrm{CH_3}}{\mathrm{C}}{=}\mathrm{CH}\underset{\mathrm{Ph}}{\mathrm{C}}{=}\mathrm{NPh} + \mathrm{PhNHMgX} \qquad (1)$$

Hydrazones behave somewhat analogously to imines. Some aldehyde phenylhydrazones add Grignard reagents, but the NH proton destroys 1 mole of reagent and the reactions are accompanied by N–N cleavage and are not clean.[2] Benzophenone phenylhydrazone does not undergo addition at all.[4] Some dimethylhydrazones have been reported to undergo normal addition of butyllithium or phenyllithium to give trisubstituted hydrazines,[2] but many examples failed altogether and the highest yield reported was only 32%. The reaction of quaternary hydrazonium salts $R_2C{=}NN^+R_3\,X^-$ with organometallic reagents has not been reported before and is the subject of this paper. The sluggishness of the carbon–nitrogen double bond of imines toward addition of Grignard reagents is largely overcome in immonium salts, $R_2C{=}N^+R_2\ X^-$, which give good yields of tertiary amines.[6] In view of this, we expected that the inductive effect of the positive charge of quaternary hydrazonium salts would activate the azomethine system toward addition reactions. However, this expectation was not realized; this exploratory paper charts the principal types of reaction that actually take place.

Results

Quaternary hydrazonium iodides of benzophenone, *p,p*′-dichlorobenzophenone, *p,p*′-dimethoxybenzophenone, and *p*-chlorobenzaldehyde were prepared by treating the corresponding dimethylhydrazones or pentamethylenehydrazones with methyl iodide.[7]

Treatment of benzophenone trimethylhydrazonium iodide with phenylmagnesium bromide, methylmagnesium iodide, or methyllithium in ether resulted in marked heat evolution, but quaternary hydrazonium salt could be recovered upon hydrolysis, nearly quantitatively in the case of the Grignard reagents. Only when a threefold excess of Grignard reagent and a reaction time of 10 hr in refluxing ether were used was extensive further reaction observed with phenylmagnesium bromide. Hydrolysis led to the recovery

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[1] Taken from the doctoral thesis of H. H. Tan, University of Michigan, 1962.

[2] A. Marxer and M. Horvath, *Helv. Chim. Acta*, **47**, 1101 (1964).

[3] W. F. Short and J. S. Watt, *J. Chem. Soc.*, 2293 (1930).

[4] H. Gilman, J. E. Kirby, and C. R. Kinney, *J. Am. Chem. Soc.*, **51**, 2252 (1929).

[5] H. Gilman and J. Morton, *ibid.*, **70**, 2514 (1948).

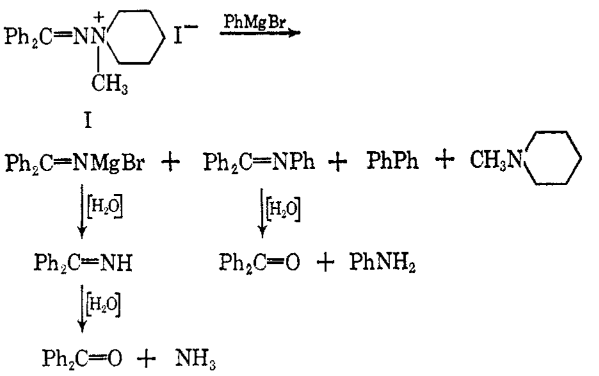
[6] D. Craig, *ibid.*, **60**, 1458 (1938); E. Bergmann and W. Rosenthal, *J. Prakt. Chem.*, [2] **135**, 267 (1932); H. G. Reiber and T. D. Stewart, *J. Am. Chem. Soc.*, **62**, 3026 (1940).

[7] P. A. S. Smith and E. E. Most, Jr. *J. Org. Chem.*, **22**, 359 (1957).

of trimethylamine, biphenyl (65%), and benzophenone (73%), but no evidence for addition at the azomethine system was obtained. Thereafter, tetrahydrofuran was used in place of ether in most experiments in order to hasten the reaction by the use of higher temperatures and methylpentamethylenehydrazonium salts (derived from N-aminopiperidine) were used instead of trimethylhydrazonium salts because of easier preparation and isolation of products. Furthermore, it was found that the tertiary amine (N-methylpiperidine) was already present in the reaction mixture before hydrolysis and could be distilled out beforehand.

Benzophenone methylpentamethylenehydrazonium iodide (I) reacted with phenylmagnesium bromide in ether in essentially the same manner as the trimethylhydrazonium analog, but by use of very mild hydrolysis conditions in the work-up, benzophenonimine could be isolated as the precursor of the benzophenone.

A similar experiment carried out in refluxing tetrahydrofuran gave rise to aniline, isolated in 4% yield as benzanilide, in addition to benzophenone (79%), biphenyl (50%), and N-methylpiperidine (73%) (isolated as hydrobromide and/or N-benzyl-N-methylpiperidinium chloride). These results may be summarized by eq 2. Benzophenone pentamethylenehydrazone (the unquaternized precursor of I) did not react with phenylmagnesium bromide in refluxing ether; it was recovered in 84% yield, along with benzophenone (15%) and N-aminopiperidine resulting from hydrolysis during work-up.



$Ph_2C{=}NMgBr + Ph_2C{=}NPh + PhPh + CH_3N\langle\ \rangle$ (2)

$Ph_2C{=}NH \qquad Ph_2C{=}O + PhNH_2$

$Ph_2C{=}O + NH_3$

A series of experiments was carried out with I and various Grignard reagents (used in excess). The pattern of products was similar in each case. Tertiary amine was first removed by distillation, the residual reaction mixtures were neutralized with saturated ammonium chloride, and the basic components were then precipitated with dry hydrogen chloride. Although benzophenonimine was in some cases isolated as its hydrochloride in good yield by this method, it was in many cases mixed with lesser amounts of the N-substituted imine. Since separation was difficult, the composition of such mixtures was more reliably determined by complete hydrolysis to give benzophenone and a mixture of ammonium chloride and primary amine hydrochloride(s), which could be either separated by extraction with absolute alcohol or analyzed by vapor phase chromatography of the free bases. The yield of benzophenonimine could thus be reckoned either from the yield of ammonium chloride or from the yield of benzophenone corrected for the amount derived from N-substituted imine. The yields of biaryl (or bialkyl) reported are high by 5–12%, that being the amount of biaryl present in the Grignard reagents as we prepared them, as determined separately. Furthermore, the yields are from weights of unrecrystallized material (see Experimental Section), which may have contained small amounts of benzophenone. The results are collected in Table I. N-Methylpiperidine was formed in every reaction, generally in yields between 80 and 90%, but the amount was not always determined precisely owing to difficulties in quantitative separation and isolation. In one case (2,4-dimethylphenylmagnesium bromide), the benzophenone N-arylimine was not precipitated along with benzophenonimine hydrochloride, but appeared in the neutral, biaryl fraction. Chromatography separated it as an orange-yellow oil, which was subsequently hydrolyzed to benzophenone and 2,4-xylidine hydrochloride.

TABLE I

REACTION OF GRIGNARD REAGENTS WITH BENZOPHENONE METHYLPENTAMETHYLENEHYDRAZONIUM IODIDE (MOLE RATIO 3:1)

Reagent, RMgBr	$Ph_2C{=}NH$, %[a]	RNH_2, %	$PhNH_2$, %	R–R, %
Phenyl[b]	73	4	...	83
2,4-Xylyl	69[c]	27	...	72
p-Tolyl	60 (74)	10	0.2	~100
Mesityl	54 (44)	35	0.5	51
t-Butyl	80 (77)			26
p-Chlorophenyl	80 (84)	7	<0.2	89

[a] The values are from the weight of benzophenone. The values in parentheses are from the weight of ammonium chloride. [b] Mole ratio 3.3:1. [c] Weighed as imine hydrochloride.

The reaction of *t*-butylmagnesium chloride was exceptional in that reductive cleavage, which appeared to be the only reaction, led in part to benzhydrylamine instead of only to benzophenonimine. A further group of experiments was carried out with the corresponding *p,p'*-dichloro- and *p,p'*-dimethoxybenzophenone derivatives; the results are collected in Table II. One aldehyde derivative, *p*-chlorobenzaldehyde methylpentamethylenehydrazonium iodide, was examined; it reacted with *p*-tolylmagnesium bromide to produce principally *p*-chloro-*p'*-methylbenzophenone (82%, through its imine) and small amounts of *p*-toluidine (8%) and bi-*p*-tolyl (11%).

TABLE II

REACTION OF *para*-DISUBSTITUTED BENZOPHENONE METHYLPENTAMETHYLENEHYDRAZONIUM IODIDES WITH GRIGNARD REAGENTS

Substituent	R of RMgBr	$Ar_2C{=}NH$, %	RNH_2, %	$ArNH_2$, %	R–R, %
CH_3O	*p*-ClC_6H_4[a]	98[b]	0	0	98[e]
CH_3O	C_2H_5	68[c] (50)[f]	...	23	...
Cl	2,4-$(CH_3)_2C_6H_3$[a]	72[d]	18	0	47[e]
Cl	C_6H_5	72 (58)[f]	8	0	100[e]

[a] Mole ratio 3.3:1. [b] Weighed as imine hydrochloride. [c] Impure solid ketone, shown by recrystallization to consist substantially of *p,p'*-dimethoxybenzophenone; a quantity of oily, mixed ketones was obtained as well. [d] Weighed both as imine hydrochloride and as ketone. [e] Not corrected for biaryl present in the Grignard reagent. [f] Yield (per cent) of NH_4Cl.

An experiment with I was carried out in ether using phenyllithium instead of Grignard reagent, in a mole ratio of 3.3:1 of hydrazone. Reaction appeared to occur somewhat more readily, but the products followed the same pattern with one exception; triphenylcarbinol was obtained in 12% yield from hydrolysis of the precipitated mixed hydrochlorides. The other products were benzophenone (70%), ammonium chloride (69%), aniline (9%), and biphenyl (55%). An experiment with β-naphthyllithium under similar conditions apparently resulted in incomplete consumption of both reagents, even though a mole ratio of only 1.2:1 was used; both naphthalene (11%) and quaternary hydrazone (24%) were recovered, along with benzophenonimine (73%, corrected for recovered hydrazone) and bi-β-naphthyl (74%).

Discussion

The major reaction in the systems studied is clearly reductive cleavage of the N-N bond, resulting in formation of the magnesium derivative of the imine and an equivalent quantity of biaryl or bialkyl (eq 3). Indeed, under appropriate conditions the magnesium derivative can be caused to precipitate from the reaction mixture.

$$\mathrm{Ar_2C{=}N\overset{+}{N}R_3X^- + 2Ar'MgX \longrightarrow Ar_2C{=}NMgX + Ar'Ar' + R_3N + MgX_2} \quad (3)$$

Two other reactions, not necessarily independent of each other, compete with reduction; one results in attachment of the organic moiety of the Grignard reagent to the azomethine nitrogen and the other entails migration of a C-attached group to nitrogen (eq 4). A mechanistically feasible process leading to such products is addition of Ar'MgX to the azomethine group, giving an amine N-imide, which might be able to stabilize itself by C-to-N rearrangement of an aryl group (eq 5), analogous to the Stieglitz rearrangement.[8]

$$\mathrm{Ar_2C{=}N\overset{+}{N}R_3X^- + Ar'MgX \longrightarrow \begin{array}{c} Ar_2C{=}NAr' \\ or \\ ArAr'C{=}NAr \end{array} + R_3N + MgX_2} \quad (4)$$

$$\mathrm{Ar_2C{=}N\overset{+}{N}R_3X^- + Ar'MgX \longrightarrow Ar_2Ar'C\bar{N}\overset{+}{N}R_3 + MgX_2 \longrightarrow ArAr'C{=}NAr \text{ or } Ar_2C{=}NAr' + R_3N} \quad (5)$$

Indeed, we have been able to think of no other path to account for the occurrence of C to N aryl migration, the products of which were unequivocally obtained, albeit in small amounts.

If an amine N-imide were the intermediate giving rise to all of the N-substituted imine obtained, however, the relative extents of attachment of Ar and Ar' to N would be expected to be determined by migration aptitudes and the obvious 2:1 statistical factor and not on which group was originally in the Grignard reagent and which in the hydrazone. To evaluate this conclusion, the pair of experiments in which the p-chlorophenyl group is respectively in either the hydrazone or the Grignard reagent (see Tables I and II) was carried out. The group that became attached to nitrogen was in each case overwhelmingly that from the Grignard reagent ($PhNH_2/ClC_6H_4NH_2 > 100$; $ClC_6H_4NH_2/PhNH_2 = 40$), in ratios that completely obliterate the 1:2 statistical factors present. The influence of the fact that p-chlorophenyl has a markedly lower aptitude for migrating to an electron-deficient nitrogen[8] was noticeable only in the result that, when a phenyl group was originally on the azomethine carbon, it migrated to nitrogen in trace amounts, but, when a p-chlorophenyl group was there instead, the amount of migration was below detectability. Consequently, it must be concluded that a large part of the N-arylimine formed derives from a process in which the groups from the Grignard reagent and those of the azomethine carbon do not become structurally equivalent and so do not compete for the opportunity to migrate.

The amine N-imide can qualify as the intermediate for the formation of all of the N-arylimine only if it is assumed that migration to nitrogen may occur faster than rotation about the C–N bond and that the position of initial attachment is the most favorable one rotationally for migration of the added group. The alternative is some form of direct substitution on the azomethine nitrogen. Such a process might be a one-step nucleophilic displacement of R_3N by Ar' within the coordination sphere of Mg, a multistep process involving intermediates in the reductive cleavage reaction, perhaps $Ar_2C{=}N^-$ and Ar'^+, or $Ar_2C{=}N\cdot$ and $Ar'\cdot$. Although reasons can be invoked to favor or disfavor a particular possibility, a more intensive investigation is needed before a clear choice can be made.[9]

The reaction of ethylmagnesium bromide with the quaternary hydrazone of dimethoxybenzophenone (Table II) is exceptional for giving an unusually large amount of amine derived from C to N migration. This experiment was, indeed, selected in that expectation and its result is good evidence for an amine N-imide intermediate as precursor of part of the N-arylimine. The relatively small ethyl group might more readily penetrate to the point of attachment to the azomethine carbon and its migration aptitude is low whereas that of the competitor, p-anisyl, is very high. Further evidence for the intermediacy of an amine N-imide is found in the appearance of triphenylcarbinol in the reaction of phenyllithium with the quaternary hydrazone of benzophenone. It is significant that this product was obtained upon hydrolysis of the mixed hydrochlorides of the basic products; presumably the triphenylmethyl group was originally attached to nitrogen, probably as triphenylmethylamine or triphenylmethylaniline. This experiment was carried out in ether and thus at a lower temperature, at which C to N migration might have been incomplete.

In the reaction of the p-chlorobenzaldehyde quaternary hydrazone, which produced largely the imine of an unsymmetrical ketone, it is possible that an amine N-imide was an intermediate, but the Grignard reagent might instead have functioned at first primarily as a base, bringing about elimination of tertiary amine to form a nitrile (eq 6). This behavior has

$$\mathrm{ArCH{=}N\overset{+}{N}R_3X^- + Ar'MgX \longrightarrow ArCN + R_3N + Ar'H + MgX_2} \quad (6)$$

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[8] P. A. S. Smith, "Molecular Rearrangements," P. de Mayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 8.

[9] A further question is whether the initial exothermic reaction consists of coordination between the metal and the hydrazone moiety or, as a referee has suggested, an acid–base reaction at the N-methyl group, leading to an ylide. The answer to this question does not alter the following discussion, but we believe the observed formation of tertiary amine in the free state before hydrolysis is evidence that the initial reaction does not involve ylide formation (which would not produce free tertiary amine, but its metal derivative R_2NCH_2MgX).

TABLE III

PENTAMETHYLENEHYDRAZONES AND N-METHYLPENTAMETHYLENEHYDRAZONIUM IODIDES OF BENZOPHENONES, $(p\text{-}RC_6H_4)_2C{=}O$

	Pentamethylenehydrazone			Methiodide		
R	Yield, %	Bp, °C (mm)	Registry no.	Yield, %	Mp (dec), °C	Registry no.
H	100[a]	135 (0.15)		80[b]	171	13134-23-1
CH_3O	90[c]	83–85	13134-21-9	73[d]	153	13134-24-2
Cl	89	Oil[e]	13134-22-0	74[f]	165	13134-25-3

[a] *Anal.* Calcd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: C, 81.75; H, 7.53; N, 10.54. [b] *Anal.* Calcd for $C_{19}H_{23}N_2I$: C, 56.16; H, 5.70; , 6.90. Found: C, 56.20; H, 5.67; N, 6.98. [c] *Anal.* Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.87; H, 7.56; N, 8.54. [d] *Anal.* Calcd for $C_{21}H_{27}N_2O_2I$: C, 54.07; H, 5.84; N, 6.00. Found: C, 53.99; H, 5.86; N, 5.98. [e] Not distilled. [f] *Anal.* Calcd for $C_{19}H_{21}Cl_2IN_2$: C, 48.02; H, 4.46; N, 5.90. Found: C, 48.10; H, 4.43; N, 5.99.

recently been reported as a general reaction with bases.[10] Subsequent reaction of the nitrile with more Grignard reagent would lead to the unsymmetrical ketone obtained. The reactions observed with ketone derivatives evidently accompanied the foregoing process, but only to a minor extent.

Experimental Section[11]

Materials.—N-Aminopiperidine was prepared by the lithium aluminum hydride reduction of N-nitrosopiperidine.[12] *p,p'*-Dichlorobenzophenone was prepared from technical grade DDT.[13] 2,4-Dimethylbromobenzene[14] and 2,4,6-trimethylbromobenzene[15] were prepared by bromination of the corresponding hydrocarbons. β-Naphthyl bromide was prepared from β-naphthol and phosphorus pentabromide.[16] Benzophenone N,N,N-trimethylhydrazonium iodide was prepared from the dimethylhydrazone and methyl iodide.[7] Other materials were obtained from commercial sources.

Pentamethylenehydrazones and N-Methylpentamethylenehydrazonium Iodides.—These substances were all prepared in essentially the same manner, as exemplified by the benzophenone derivatives described here. The yields and properties are collected in Table III. A mixture of 182.2 g (1.00 mole) of benzophenone, 110 g (1.10 mole) of N-aminopiperidine, 4 ml of glacial acetic acid, 10 drops of concentrated hydrochloric acid, and 350 ml of benzene was stirred and boiled in a flask provided with a Friedrichs condenser and a Dean–Stark water separator. After 19–20 ml of water had separated, the mixture was cooled, 100 ml of benzene was added, and the whole was washed successively with water, 10% potassium carbonate solution, and water and dried over solid potassium carbonate. The solvent was removed at the water pump, leaving a yellow-orange residue of benzophenone pentamethylenehydrazone, 263 g (100%). Distillation at 135° (0.15 mm) gave a yellow oil with only small mechanical losses.

The entire quantity of pentamethylenehydrazone was dissolved in 350 ml of absolute alcohol and 150 ml of benzene and 200 ml was distilled away at atmospheric pressure to remove traces of water. Methyl iodide was purified by drying over potassium carbonate and distilling through a long column packed with bright copper turnings and 284 g (2.0 moles) was added. The mixture was refluxed for 40 hr and then cooled. The crystals that separated weighed 324 g (80%), mp 168° dec, after washing with alcohol–ether mixture; recrystallization from absolute alcohol with the help of added ether gave an analytical sample, mp 171° dec.

By a similar procedure, *p*-chlorobenzaldehyde pentamethylenehydrazone, mp 59–60°, was prepared in 97% yield. *Anal.* Calcd for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.86; H, 6.76; N, 12.65. The methiodide, mp 162° dec, was obtained from this in 82% yield. *Anal.* Calcd for $C_{13}H_{18}ClIN_2$: C, 42.82; H, 4.97; N, 7.69. Found: C, 42.93; H, 5.07; N, 7.91.

Reaction of Methylmagnesium Iodide with Benzophenone Trimethylhydrazonium Iodide.—A solution of methylmagnesium iodide was prepared from 2.43 g (0.10 g atom) of magnesium and 14.2 g of methyl iodide in 200 ml of ethyl ether. The cold solution was blanketed with nitrogen and 36.7 g (0.10 mole) of finely divided benzophenone trimethylhydrazonium iodide was added; the mixture became warm and the solid turned to a viscous syrup. The mixture was then refluxed for 5 hr, cooled in an ice bath, and hydrolyzed with cold, saturated ammonium iodide solution. The viscous material solidified and was then washed with dilute hydriodic acid and with several portions of ice water. After drying *in vacuo*, it weighed 35.2 g (96%), mp 161–165°; recrystallization from absolute ethanol by addition of ether raised the melting point to 167–169°, undepressed by admixture with starting material.

Experiments with phenylmagnesium iodide or bromide gave similar results. When methyllithium was used and the temperature held at −40° for 3 hr before warming to room temperature and hydrolyzing, most of the quaternary hydrazone was recovered contaminated with some lithium iodide. Recrystallization from methanol–ether mixture eventually gave pure quaternary hydrazone, mp 172° dec, in 20% yield, but the losses were great and the figure is not very meaningful.

Phenylmagmesium Bromide and Benzophenone N-Methylpentamethylenehydrazonium Iodide.—A mixture of 0.45 mole of phenylmagnesium bromide (prepared from 70.7 g of bromobenzene) and 40.6 g (0.10 mole) of benzophenone N-methylpentamethylenehydrazonium iodide in 250 ml of ether was refluxed for 28 hr under nitrogen. The mixture became homogeneous at first, but after a few hours a yellow solid separated. The mixture was then cooled and filtered; the precipitate weighed 23.2 g (82% as benzhydrylideniminomagnesium bromide) after washing with ether. Treatment with ice-cold concentrated hydrochloric acid converted it to colorless, crystalline benzophenonimine hydrochloride, which sublimed at 240–260°. *Anal.* Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.74; H, 5.78; N, 6.55. Hydrolysis in warm, dilute hydrochloric acid gave benzophenone.

Distillation of the ethereal filtrate left 13.2 g (38%) of biphenyl, mp 66–69°, mmp 69–70°. The distillate contained N-methylpiperidine, part of which was isolated by treatment with benzyl chloride to give N-benzyl-N-methylpiperidinium chloride, mp 244° dec. *Anal.* Calcd for $C_{13}H_{20}ClN$: C, 69.15; H, 8.93; N, 6.21. Found: C, 69.20; H, 8.70; N, 6.33.

Reaction of Phenyllithium with Benzophenone N-Methylpentamethylenehydrazonium Iodide (I).—To a solution of phenyllithium prepared[17] from 47.1 g (0.30 mole) of bromobenzene in 325 ml of ethyl ether was added 40.6 g (0.10 mole) of I in small portions and the mixture was refluxed with stirring for 20 hr under nitrogen. After removal of the N-methylpiperidine as in the foregoing experiments, the residue was diluted with 500 ml of fresh ether, cooled, and treated with chilled, saturated ammonium chloride solution. Some solid that separated was removed and the ether layer was separated, washed with a little water to remove traces of ammonia, and dried over potassium carbonate. Hydrogen chloride was passed in until saturation, which precipitated a gummy mass of hydrochlorides. The ethereal filtrate from this left 8.5 g (55%) of biphenyl, mp 60–66° (raised to 68–70°, undepressed by an authentic sample, by recrystallization from petroleum ether, bp 60–75°).

The gummy hydrochlorides were boiled with 100 ml of 1.7%

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[10] R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962).

[11] Melting points are corrected; boiling points are uncorrected. Analyses were by Spang Microanalytical Laboratory and by Micro-Tech Laboratories. Infrared spectra were recorded on a Perkin-Elmer Model 21 instrument.

[12] C. Hanna and F. W. Schueler, *J. Am. Chem. Soc.*, **74**, 3693 (1952).

[13] H. L. Haller, P. D. Bartlett, N. L. Drake, M. S. Newman, S. J. Cristol, C. M. Eaker, R. A. Hayes, G. W. Kilmer, B. Magerlein, G. P. Mueller, A. Schneider, and W. Wheatley, *ibid.*, **67**, 1591 (1945).

[14] R. W. Maxwell and R. Adams, *ibid.*, **52**, 2962 (1930).

[15] L. I. Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 95.

[16] A. Michaelis, *Ann.*, **321**, 246 (1902).

[17] R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 353 (1951).

hydrochloric acid for 30 min and the mixture was then cooled and extracted with three 100-ml portions of benzene. The dried (Na_2SO_4) and concentrated benzene extracts were chromatographed on alumina, from which 12.6 g (70%) of benzophenone, mp 46–48°, was eluted with petroleum ether–benzene mixture. Benzene then eluted 3.1 g (12%) of triphenylcarbinol, mp 156–159° (162–163° after recrystallization from chloroform–petroleum ether mixture; undepressed by an authentic sample). Evaporation of the aqueous hydrolysate left 5.2 g of solid residue, which was then extracted with cold absolute alcohol. There was left 3.8 g (69%) of ammonium chloride. Evaporation of the extracts left 1.3 g of solid, which was converted to 1.8 g (9%) of benzanilide, mp 151–155° (158–159°, undepressed by an authentic sample, after recrystallization from aqueous ethanol), by treatment with benzoyl chloride and alkali.

Reaction of β-Naphthyllithium with I.—A solution of β-naphthyllithium prepared from 24.8 g (0.12 mole) of β-bromonaphthalene in 100 ml of ethyl ether was combined with a suspension of 40.6 g (0.10 mole) of I in 100 ml of ether and refluxed under nitrogen for 60 hr. The mixture was cooled and 9.7 g (24%) of unreacted I, mp 162° dec (170°, undepressed by an authentic sample, after recrystallization from alcohol–ether mixture), was filtered off. The filtrate was stirred with ice-cold, dilute hydrochloric acid, which precipitated 12.0 g (73% after correction for recovered hydrazone) of nearly pure benzophenonimine hydrochloride, which sublimed at 245–260° (no prior liquefaction when mixed with an authentic sample). The ethereal layer of the filtrate was washed with water, dried over potassium carbonate, and evaporated, leaving a solid residue. Sublimation of this gave 1.54 g (10%) of naphthalene, mp 80–81°, undepressed by an authentic sample. The nonvolatile residue was crystallized from ethyl acetate and gave 11.2 g (58% based on hydrazone consumed, 74% on β-bromonaphthalene) of 2,2′-binaphthyl, mp 183–184° (lit.[18] mp 186°). Identification was confirmed by analysis of a sample recrystallized from ethyl acetate: mp 185–186°. *Anal.* Calcd for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.35; H, 5.49.

Reactions of Grignard Reagents with Quaternary Hydrazones in Tetrahydrofuran.—A representative example is the reaction of *p*-tolylmagnesium bromide with I. The Grignard reagent was prepared from 77.0 g (0.45 mole) of *p*-bromotoluene, 10.9 g (0.45 g atom) of magnesium, and 250 ml of tetrahydrofuran, and 60.9 g (0.15 mole) of I was added in small portions, The mixture was refluxed under nitrogen for 17 hr and approximately two-thirds of the solvent was then distilled off. Ether (400 ml) was added and distilled into the same receiver, followed by a second portion, which was also distilled. The combined distillates were diluted with a further 300 ml of ether and then saturated with hydrogen bromide, which precipitated 20.3 g (75%) of N-methylpiperidine hydrobromide, mp 184–186° (lit.[19] mp 182–184°).

The distillation residue was diluted with 500 ml of fresh ether, chilled, and hydrolyzed with cold, saturated ammonium chloride solution. A small amount of I separated and was filtered off. The filtrate was dried (K_2CO_3) and then saturated with hydrogen chloride, which generated a heavy precipitate of mixed hydrochlorides (25.1 g) which sublimed at 240–278°. Evaporation of the filtrate left 29.1 g (106%) of crude *p,p*′-bitolyl, mp 111–118°; recrystallization of a sample from light petroleum ether gave only bitolyl, mp 120–121°, undepressed by an authentic sample. The precipitated hydrochlorides were boiled with 5 ml of concentrated hydrochloric acid in 150 ml of water. After cooling, the mixture was extracted with three 100-ml portions of ether, which were combined and dried over potassium carbonate. Evaporation left 19.1 g (70%) of benzophenone, mp 46–48°, undepressed by an authentic sample.

Evaporation of the aqueous layer from the foregoing hydrolysis left 9.05 g of mixed hydrochlorides. Extraction with 100 ml of cold absolute alcohol left a residue of 5.95 g of ammonium chloride, identified by the absence of charring in a flame and by a positive test with Nessler's reagent. Evaporation of the extracts left 2.68 g of amine hydrochlorides, from which the free bases were liberated with strong potassium carbonate solution and extracted with several portions of ether. The solution was concentrated by distilling through a fractionating column; the undistilled portion was examined by vapor phase chromatography and found to contain, besides ether, only *p*-toluidine and aniline, in a ratio of 56:1. The bulk of the concentrated solution was treated with excess acetic anhydride and evaporated to dryness *in vacuo*. The residue of crude acet-*p*-toluidide, 2.25 g (10%), mp 139–144°, was recrystallized from aqueous methanol; it then had mp 146–148° (lit.[20] mp 147°). Treatment of the ethereal distillates with hydrogen bromide precipitated 0.12 g (0.4%) of N-methylpiperidine hydrobromide, mp 183–185°.

The other experiments in this category were carried out in a similar manner, with minor variations to suit the properties of the substances at hand; the results are reported in Tables I and II. A common variation was to precipitate the imine hydrochlorides with very cold, 10% aqueous hydrochloric acid. In one such experiment, using *p*-chlorophenylmagnesium bromide and the quaternary hydrazone of *p,p*′-dimethoxybenzophenone, the crude imine hydrochloride of the latter ketone was isolated in 98% yield; recrystallization from absolute alcohol–ether mixture gave a pure sample, mp 221° dec. *Anal.* Calcd for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.82; N, 5.04. Found: C, 64.93; H, 5.91; N, 5.05. In the reaction of 2,4-dimethylphenylmagnesium bromide with *p,p*′-dichlorobenzophenone quaternary hydrazone, aqueous hydrochloric acid apparently precipitated only the imine hydrochloride and not its N-aryl derivative. The latter was found among the neutral products and was separated from 2,2,4,4′-tetramethylbiphenyl by chromatography as a viscous yellow-orange oil in 18% yield. When efforts to crystallize it or its hydrochloride failed, it was hydrolyzed with hot dilute hydrochloric acid; only *p,p*′-dichlorobenzophenone, mp 144–145°, and 2,4-xylidine (*p*-nitrobenzoyl derivative, mp 169–170°, undepressed by an authentic sample) were obtained.

Reaction of *p*-Tolylmagnesium Bromide with *p*-Chlorobenzaldehyde N-Methylpentamethylenehydrazonium Iodide.—The reaction between the Grignard reagent from 10.9 g (0.45 g-atom) of magnesium and 77.0 g (0.45 mole) of *p*-bromotoluene with 77.0 g (0.21 mole) of quaternary hydrazone was carried out in tetrahydrofuran as described for the benzophenone analog. The products were N-methylpiperidine hydrobromide (23.2 g, 86%), mp 177–181°, bi-*p*-tolyl (4.40 g, 11%), mp 112–118° (mp 120–121° after one recrystallization), and 48.4 g of mixed hydrochlorides. Hydrolysis of the last in dilute hydrochloric acid yielded 39.5 g (82%) of *p*-chloro-*p*′-methylbenzophenone, mp 123–126° (lit.[21] mp 118°). Recrystallization from alcohol gave an analytical sample, mp 126–128°. *Anal.* Calcd for $C_{14}H_{11}OCl$: C, 72.88; H, 4.81; Cl, 15.37. Found: C, 73.00; H, 5.02; Cl, 15.42. An oxime prepared from it had mp 152.5–154.5°. *Anal.* Calcd for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.93; N, 5.70. Found: C, 68.70; H, 5.19; N, 5.74.

Evaporation of the aqueous phase from the hydrolysis gave 7.48 g of hydrochlorides; extraction with absolute alcohol left 5.90 g (73%) of ammonium chloride. The extract left 1.50 g of residue upon evaporation, from which the free bases were liberated with strong potassium carbonate solution and extracted into ether. Vapor phase chromatography of a sample of the concentrated extracts showed a large peak corresponding to *p*-toluidine and a very small one corresponding to N-methylpiperidine. Acetylation of the bulk of the extracts with acetic anhydride gave 1.70 g (8%) of acet-*p*-toluidide, mp 139–145° (146–148° after recrystallization from aqueous methanol).

Attempted Reaction of Phenylmagnesium Bromide with Benzophenone Pentamethylenehydrazone.—A solution of phenylmagnesium bromide (prepared from 52.3 g (0.33 mole) of bromobenzene) and 26.4 g (0.10 mole) of benzophenone pentamethylene hydrazone in 250 ml of tetrahydrofuran was refluxed under nitrogen for 50 hr. The mixture was then cooled and diluted with 100 ml of ethyl ether, which precipitated a yellow-green material. While stirring, 19 g of solid ammonium chloride was added and stirring was continued for 3 hr. The mixture was filtered and the solid was dissolved in water and extracted with ether. The combined ether phases were shaken with 150 ml of very cold 10–15% hydrochloric acid. The aqueous layer was carefully neutralized with solid potassium carbonate and then extracted with three 100-ml portions of ether. Distillation of the combined, dried (K_2CO_3) extracts gave 0.6 g (6%) of N-aminopiperidine, bp 58–59° (16 mm), and 22.2 g (84%) of benzophenone pentamethylenehydrazone, bp 130–136° (0.3 mm). From the original ethereal extract from the acidic solution was obtained 2.72 g (15%) of benzophenone, mp 40–45° (47–48° after recrystallization from ethanol).

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[18] H. Meyer and A. Hofmann, *Monatsh.*, **37**, 709 (1916).

[19] F. Kroehnke and K. Fasold, *Ber.*, **B67**, 656 (1934).

[20] W. Kelbe, *ibid.*, **16**, 1199 (1883).

[21] W. D. Cohen and J. Böeseken, *Rec. Trav. Chim.*, **38**, 113 (1919).

Registry No.—Benzophenone pentamethylenehydrazone, 13134-20-8; benzophenonimine hydrochloride, 5319-67-59; N-benzyl-N-methylpiperidinium chloride, 13127-28-1; 2,2′-binaphthyl, 612-78-2; *p,p*′-dimethoxybenzophenone, 90-96-0; *p,p*′-dichlorobenzophenone, 90-98-2; *p*-chloro-*p*′-methylbenzophenone, 5395-79-9; *p*-chloro-*p*′-methylbenzophenone oxime, 13134-28-6; acet-*p*-toluidide, 103-89-9; N-aminopiperidine, 2213-43-6; benzophenone, 119-61-9; *p*-chlorobenzaldehyde pentamethylenehydrazone, 13134-29-7.

Organic Disulfides and Related Substances. XXII. Substituted Benzyl 2-(*n*-Decylamino)ethyl Disulfide Hydrochlorides. A Possible Neighboring-Group Effect Involving Sulfur[1a,b]

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Unsymmetrical disulfides of structure 2 have been synthesized; for their purification, chromatography on specially prepared acidic alumina was necessary. Thermally induced disproportionation of these disulfides appears to be kinetically first order. The relative disproportionation rates are correlated by the Hammett σ^-, ρ relationship; $\rho = 1.1$. These data and other evidence are interpreted in terms of disulfide cleavage which involves stabilization of an incipient benzylthiolate anion by the phenyl ring and, in addition, anchimeric assistance to the cleavage by the neighboring amino group; the possible influence of similar factors on the stability of biochemically important disulfide linkages seems worth considering. Although the symmetrical disulfides are soluble in 95% ethanol, disproportionation proceeds virtually to completion and cannot be significantly reversed.

In a previous paper, we reported synthesis and disproportionation of a series of *para*-substituted 2-(aryldithio)ethylamine hydrochlorides (**1**).[2] Studies of

$$p\text{-XC}_6\text{H}_4\text{SS(CH}_2)_2\text{NH}_3{}^+\text{Cl}^-$$

1

disproportionation now have been extended to a series of *meta*- and *para*-substituted benzyl 2-(*n*-decylamino)ethyl disulfide hydrochlorides (**2**) The preparation and investigation of the benzyl derivatives had a threefold purpose: (a) to learn whether any correlations with the previous aryldithio series (**1**) could be found; (b) to examine the possibility of anchimeric assistance by the benzene ring; and (c) to see what effect, if any, the long side chain would have on the antiradiation activity of these compounds (it was thought that the long side chain might facilitate passage of the molecule through membrane barriers).

The compounds were prepared essentially as were those of series **1**,[2] but by reaction of an arylmethanethiol with 2-(*n*-decylamino)ethyl 2-(*n*-decylamino)ethanethiolsulfonate dihydrochloride, as is shown in eq 1.[3] In preparing disulfides of structure **1**, we isolated the unsymmetrical disulfide by extracting unchanged thiol, making the reaction mixture alkaline, extracting the free base into an organic solvent, and reconverting it to the salt by treatment with HCl.[2] This procedure failed with disulfides of structure **2** owing to gel formation Good results were obtained, however, by chromatographing the crude reaction mixture on acid-washed alumina and eluting with chloroform. It is noteworthy that first trials using this procedure sometimes gave erratic results, which we attribute to excessively basic alumina This problem was resolved by treating the alumina in chloroform with HCl. Preparative results are shown in Table I. As before,[2] the products were well-defined crystalline compounds with sharp melting points and all showed only one spot on thin layer chromatography. In contrast to the aryldithio series (**1**), the compounds were insoluble in water but readily soluble in chloroform and dioxane; two (**7**, **10**) even showed some degree of solubility in ether, a property utilized to follow their disproportionation.

$$\begin{aligned}&m\text{- or }p\text{-XC}_6\text{H}_4\text{CH}_2\text{SH} + \\ &\quad \text{Cl}^-\ n\text{-C}_{10}\text{H}_{21}\text{NH}_2{}^+(\text{CH}_2)_2\text{SO}_2\text{S}(\text{CH}_2)_2\text{NH}_2{}^+\text{-}n\text{-C}_{10}\text{H}_{21}\ \text{Cl}^- \longrightarrow \\ &\qquad n\text{-C}_{10}\text{H}_{21}\text{NH}_2{}^+(\text{CH}_2)_2\text{SO}_2\text{H Cl}^- + \\ &\qquad\quad m\text{- or }p\text{-XC}_6\text{H}_4\text{CH}_2\text{SS}(\text{CH}_2)_2\text{NH}_2{}^+\text{-}n\text{-C}_{10}\text{H}_{21}\ \text{Cl}^- \qquad (1)\end{aligned}$$

2, X = substituent
3, X = H
4, X = p-CH$_3$
5, X = p-CH$_3$O
6, X = p-Cl
7, X = p-NO$_2$
8, X = p-CN
9, X = m-NO$_2$
10, X = m-CN

In order to study thermal disproportionations, ethanolic solutions of the disulfides were heated at 100° in sealed ampoules protected from light by aluminum foil. We reported evidence for the aryldithio series (**1**) that the disproportionation is largely heterolytic under these conditions.[2] The kinetics of disproportionation of the benzyl disulfides (**2**) were followed by determining the amount formed of the symmetrical disulfide **11** or **12** (eq 2). All of the symmetrical benzyl

$$\mathbf{2} \longrightarrow {}^1\!/_2(m\text{- or }p\text{-XC}_6\text{H}_4\text{CH}_2\text{S-})_2 + {}^1\!/_2(\text{Cl}^-\ n\text{-C}_{10}\text{H}_{21}\text{NH}_2{}^+\text{CH}_2\text{CH}_2\text{S-})_2 \qquad (2)$$

11 **12**

disulfides (**11**) were soluble in ether and some of them in hexane, while most of the hydrochlorides of type **2** or **12** were insoluble in these solvents. However, the *p*-nitro (**7**) and *m*-cyano (**10**) derivatives were somewhat soluble in ether, and hexane could not be used because their corresponding symmetrical benzyl disulfides (**11**)

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[1] (a) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (b) Paper XXI: J. D. Buckman, M. Bellas, H. K. Kim, and L. Field, *J. Org. Chem.*, **32**, 1626 (1967). (c) To whom correspondence should be addressed.

[2] L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966).

[3] Some of the arylmethanethiols were obtained by reaction of the corresponding benzyl halides with thiourea. Hydrolysis of the benzylthiuronium salts to the thiols was achieved by brief treatment with aqueous sodium hydroxide, acidification, and extraction. This procedure avoids the prolonged boiling often used, which is likely to lead to more by-products (see Experimental Section).