Reactions of Vicinal Dianions. The Alkylation of the Benzophenone Anil Dianion

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Reduction of benzophenone anil (1) with alkali metals produces a vicinal dianion 2. The alkylation of this dianion with isopropyl halides is studied as a function of alkali metal (Li, Na, K), solvent (THF, DEE), and amount (1 and 2 equiv) and kind of isopropyl halide (Cl, Br, I). The alkylation product consists of a mixture of 2-methyl-*N*,1,1-triphenylpropylamine (3), *N*-(*o*- and *p*-isopropylbenzhydryl)aniline (4), *o*- and *p*-isopropylbenzophenone anil (5), *N*-(2,5-diisopropylbenzhydryl)aniline (6), and 2,5-diisopropylbenzophenone anil (7). The exact composition varies over a wide range depending on the reaction conditions. The most reactive halide, isopropyl iodide, produces the largest amount of alkylation in the aromatic ring and, if 2 equiv are present, also produces the largest amount of dialkylation. The cation associated with 2 also exerts a marked influence; while large amounts of ortho alkylation occur with lithium as cation, essentially only alkylation at the benzylic carbon is observed when the cation is potassium. These effects are discussed.

Benzophenone anil (**1**) on reduction by alkali metals[1,2] in aprotic solvents produces a dianion **2** which has the complex and intriguing possibility of reaction at either or both of the two vicinal anionic centers. In addition to this, reaction at sites on the aromatic rings of the diphenylmethyl moiety might be anticipated by analogy with the observed behavior of other benzyl organometallic reagents.[3]

Our earlier preliminary studies[2] of the alkylation of the dianion **2** have provided examples of each of these reactions. We wish to report a detailed study of this alkylation with isopropyl halides. This study was initiated in order to determine the factors controlling the alkylation, in order to provide some understanding of the mechanism involved in the alkylation, and in order to gain some control over the synthetic utility of the reaction. The parameters selected for study were alkali metal (Li, Na, K), solvent [tetrahydrofuran (THF) and diethyl ether (DEE)], and the leaving group of the isopropyl halide (Cl, Br, I).

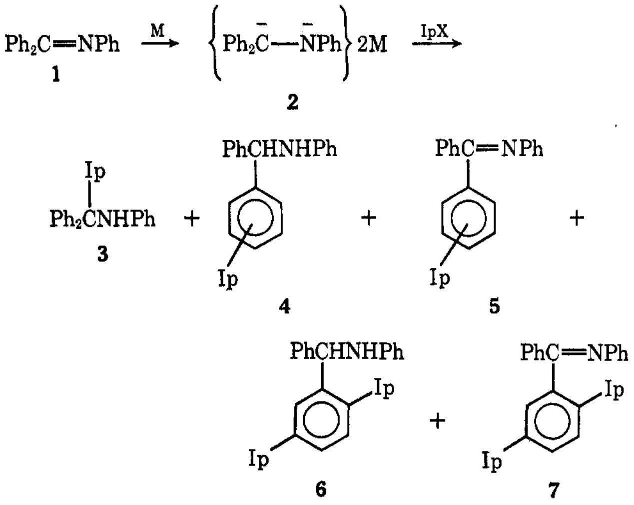
Results

A variety of alkylation products were observed, the exact product composition depending on all the parameters studied. The reaction mixtures were analyzed by vapor phase chromatography (vpc) and the individual components were identified by isolation, by vpc retention time, and/or by conversion to and identification of a derivative. Scheme I summarizes the products observed.

In addition to the compounds shown in Scheme I, two others were detected by vpc. One of these, unknown C, had the largest retention time of any compound observed and probably contains two isopropyl groups. Since it was formed in small amounts and only when DEE solutions of the dianion **2** were used, no attempt was made to characterize it. The other compound, unknown A, was generally formed together with compound **7**. Several attempts to isolate this compound were unsuccessful. Since it was observed that unknown A was completely converted to **7** on brief contact with aqueous acid and also was converted to **6** by reduction, this compound is considered to be the less stable of the syn–anti pair of compounds **7**, formed under the nonequilibrating alkaline (or neutral) conditions of the alkylation reaction.

SCHEME I

PRODUCTS FROM THE ALKYLATION REACTION



Ip = isopropyl

One additional compound was detected which is not shown in Scheme I, *m*-isopropylbenzophenone anil (**5**, *m*-Ip). Originally, the dialkylated products were thought to be the *m*-isopropyl analogs of **4** and **5** and authentic samples were prepared.[4] This synthesis was not entirely in vain, since a very minor product proved to have an identical retention time as **5** (*m*-Ip) and from the hydrolysis products *m*-isopropylbenzophenone was isolated by preparative vpc. However, the quantities of this material are so minor (*ca.* 1%) that it has been omitted from the discussion (see ref 15).

While nitrogen alkylation has been effected by methyl iodide,[2a] no *N*-isopropylbenzhydrylaniline was detected among the reaction products. The absence of any "C,-N-diisopropylated" product was indicated[2] by the absence of any *N*-isopropylaniline among the compounds formed on heating the reaction mixtures with aqueous HCl. Finally, protonation of the dianion **2** with 1

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[1] (a) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 281 (1928); (b) B. M. Mikhailov and K. N. Kurdyumova, *J. Gen. Chem. USSR*, **26**, 899 (1956).

[2] (a) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2245 (1966); (b) J. G. Smith, *ibid.*, **46**, 2271 (1968); (c) R. Turle and J. G. Smith, *Tetrahedron Lett.*, 2227 (1969).

[3] (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, p 1134; (b) R. A. Benkeser and T. E. Johnston, *J. Amer. Chem. Soc.*, **88**, 2220 (1966); (c) R. A. Benkeser and W. De Talvo, *ibid.*, **89**, 2141 (1967); (d) R. A. Benkeser, T. E. Johnston, and W.-H. Tong, *J. Org. Chem.*, **33**, 2203 (1968); (e) G. A. Russell, *J. Amer. Chem. Soc.*, **81**, 2017 (1959).

[4] We are indebted to Mr. R. Pearce who synthesized this series of compounds as part of an undergraduate research project.

TABLE I

SUBSTITUTION PATTERN IN THE ALKYLATION OF THE BENZOPHENONE ANIL DIANION (2)

			Position of entering isopropyl group											
			% 3 (benzylic)			% 4 + 5 (*o*-Ip)			% 4 + 5 (*p*-Ip)			% 6 + 7 (di-Ip)		
Solvent	Metal	IpX, equiv	X = Cl	Br	I	Cl	Br	I	Cl	Br	I	Cl	Br	I
THF	Li	1	46	25	22	45	57	48	9	18	30			
THF	Na	1	61	51	38	39	45	49		4	13			
THF	K	1	98	90	63	0	9	17	2	1	20			
THF	Li	2	34	25	26	57	57	11	9	18	35			25
THF	Na	2	61	64	41	39	21	9		13	18		2	32
THF	K	2	92	93	68	8	6	0		1	19			13
DEE	Na	1	60	68	52	16	14	9	12	12	39	12	6	
DEE	Na	2	60	60	46	18	14	8	12	23	45	9	3	1

equiv of *tert*-butyl alcohol followed by several attempts to alkylate the resulting anion failed; the only product isolated was *N*-benzhydrylaniline. In the case of secondary halides, dehydrohalogenation was the only observed reaction.[5]

The complete analytical data is presented in the Experimental Section (Table II) but a simpler presentation showing only the substitution patterns is given in Table I. Results obtained with the dianion **2** (M = Li) in DEE are omitted here since the solution was not homogeneous. As Kornblum[6] has shown, homogeneity can be a major variable in the alkylation of bidentate anions. A potassium dianion **2** (M = K) could not be formed in DEE.

A comparison of the products generated by 1 mol of isopropyl halide with those formed by 2 mol shows that the extent of benzylic and para alkylation is the same. When differences do occur, they do so chiefly in the formation of dialkylated products at the expense of the ortho alkylated ones. It should be noted that such a deviation occurs when the alkylating agent is isopropyl iodide or (less often) isopropyl bromide. Furthermore, this effect of the amount of alkylating agent is seen in THF but not in DEE.

The substitution pattern observed in THF with 1 mol of isopropyl halide is influenced both by the cation and by the halogen. As the cation changes, Li → Na → K, the amount of benzylic alkylation increases at the expense of all other modes of alkylation. As the halogen changes Cl → Br → I, ring alkylation (especially para) increases at the expense of benzylic alkylation (ortho alkylation remains approximately constant). In the less basic solvent, DEE, this same trend can be seen but the increase in para alkylation is accompanied by a decrease of both benzylic and ortho alkylation.

Discussion

The influence of the halogen atom upon the course of the reaction prompted consideration of an exchange reaction operating with the more reactive halides. Conceivably, the dianion **2** might react[7] with isopropyl

$$\underset{\mathbf{2}}{\{Ph_2\bar{C}-\bar{N}Ph\}2M^+} + IpI \longrightarrow MI + IpM + \underset{\mathbf{1}}{Ph_2C{=}NPh}$$

iodide (or bromide) in the manner shown. The organometallic compound (IpM) might then react with the regenerated benzophenone anil (**1**) to form the products observed.

This possibility was examined by treating **1** with isopropyllithium both with and without the subsequent addition of 1 mol of isopropyl halide; the former conditions simulated those experiments in which alkylation of **2** was effected with 2 mol of isopropyl halide. The observed alkylation pattern differs substantially from that obtained in the alkylation of dianion **2**. First, no dialkylation products were observed in the isopropyllithium experiments while they are quite prevalent in the alkylation of **2** (M = Li) and isopropyl iodide (the most likely system to undergo an exchange reaction). Second, the substitution pattern itself differs. With isopropyllithium, approximately equal amounts of benzylic, ortho, and para alkylation occur while, with **2** (M = Li) and isopropyl iodide, the product composition is heavily biased toward ortho alkylation.

It is concluded that an exchange reaction does not play a significant role in the alkylation of dianion **2**.

If this alkylation is considered to be a nucleophilic substitution of the isopropyl halide by the dianion **2**, the trends observed in this study become understandable. Delocalization of the anionic charge from the benzylic carbon into the aromatic rings[8] permits alkylation to occur at several points within the diphenylmethyl unit. Russell[3e] has reported that ring substitution in a benzylic anion became observable only when the second reagent was a reactive (and hence a nondiscriminating) one. The extent of ring alkylation, especially in the para position, increases as the reactivity of the isopropyl halide increases.

Other factors appear to control the extent of alkylation at the ortho position. By analogy with the "abnormal" reactions of Grignard reagents,[3a] one may consider a cyclic six-center transition state[9] as being responsible for this mode of attack. However, the argument of Kornblum[10] seems more appropriate. Alkylation of the benzylic position requires a moderately large separation between the metal cation and the developing halide ion. On the other hand, alkylation at the ortho position permits the metal cation and the developing halide ion to be spatially proximate. In solvents of low dielectric constant such as THF, the latter mode of reaction is favored.

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(5) Color changes indicated that a reaction was indeed occurring.

(6) N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

(7) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951). (b) A related effect of halogens has been observed; see W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).

(8) Charge delocalization in the diphenylmethyl carbanion has been reported: (a) V. R. Sandel and H. H. Freedman, *ibid.*, **85**, 2328 (1963); (b) R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Commun.*, 117 (1969).

(9) (a) J. J. Eisch, "The Chemistry of Organometallic Compounds," Macmillan, New York, N. Y., 1967, pp 54, 88; (b) H. D. Zook and J. A. Miller, *J. Org. Chem.*, **36**, 1112 (1971).

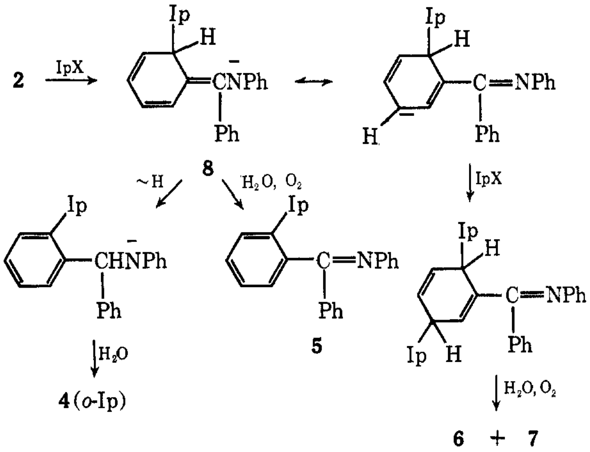
(10) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Amer. Chem. Soc.*, **85**, 1148 (1963).

As Kornblum suggests, this electrostatic constraint on the direction of alkylation will be dependent on the cation. The effect will be large with small cations forming tight ion pairs (*i.e.*, Li^+) but less effective as the cation becomes larger, the positive charge more diffuse and the ion pairs looser.

The primary product from alkylation at the ortho (or para) position is a triene such as **8** and evidence for such intermediates has been adduced by Benkeser[3c] and others.[11] Two means are available for rearomatization of these derivatives, a proton shift to form a substituted benzhydrylaniline and oxidation during isolation to form a substituted benzophenone anil (see Scheme II).

SCHEME II

RING ALKYLATION OF THE BENZOPHENONE ANIL DIANION



The former seems favored by the ortho-substituted product while the latter is favored by the para-substituted product.

In the presence of a second equivalent of isopropyl iodide, further alkylation may occur. The triene **8** is now an ambident anion and the anionic charge is delocalized over an extended conjugated system as is shown (in part) in Scheme II. A second alkylation producing disubstituted derivatives is thus a possibility.

Only with the more reactive halides (iodide) do significant amounts of dialkylation occur. With the less reactive chloride, the second alkyl group is not introduced but dehydrohalogenation predominates with the most noticeable consequence being that the para-substituted product appears now as the *N*-substituted aniline rather than the anil.

This dialkylation is confined to the ortho-substituted primary product **8**. Probably the controlling factor is steric. Analogous reasoning with the primary para product would predict the formation of 3,4-diisopropyl derivatives and the introduction of a second isopropyl group adjacent to the first would be energetically unfavorable.

Indeed, it is probably essential[12] that the dialkylated products **6** and **7** be derived from the intermediate **8**. Alternative routes involving nucleophilic substitution of **5** (*o*-Ip) or alkylation of the dianion of **5** (*o*-Ip) (formed by electron transfer from **2**) should not produce the 2,5-diisopropyl derivatives **6** and **7** but instead 2,4-, 2,6-, and compounds with the alkyl groups in different aromatic rings.

Recently, considerable attention has focused on radical intermediates in the reactions of organometallic compounds with alkyl halides.[13] Unfortunately, these mechanistic studies are directed toward aliphatic organometallic compounds or toward those that are clearly radical anions. The possibility that radical anions are intermediates in the alkylations studied here cannot be completely excluded particularly in view of a recent suggestion that electron transfer may well be the first step in nucleophilic substitution.[13i]

The presently available data on the reaction of resonance stabilized organometallic compounds with optically active alkyl halides supports a nucleophilic substitution mechanism[14] and for this reason the discussion has centered around such a mechanism. We are presently comparing the reactions of the radical anion[15] of **1** and the dianion of **1** (*i.e.*, **2**) with a number of different reagents to see what differences there may be.

Experimental Section

Melting points were determined in an open capillary using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer. Chemical shifts are reported in parts per million downfield from internal TMS (δ units). Vapor phase chromatography (vpc) was carried out on a Varian-Aerograph Model 1520 instrument equipped with flame ionization detectors (for analytical results) and thermal conductivity detectors (for preparative work). Silica gel (0.05-0.20 mm) from E. Merck AG was used for column chromatography and Eastman Chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analytical results were obtained from A. B. Gygli, Toronto, Ontario, and M-H-W Laboratories, Garden City, Mich.

Preparation and Reactions of Benzophenone Anil Dianion (2).—The preparation and handling of the dianion **2** has been described[2] elsewhere. The normal experiment utilized 0.01 mol of **2** in 70 ± 10 g of solvent (distilled from $LiAlH_4$). This solution was cooled to $-50°$ and the isopropyl halide was injected through a septum into the stirred solution. After stirring at $-50°$ for 30 min, the solution was allowed to warm to room temperature and stand for 12 hr. Water was then added and the reaction products were isolated by ether extraction.

Analysis.—No column could be found which resolved **3** and **4** (*o*-Ip). Consequently, each reaction mixture was subjected to two analyses. In the first, the reaction mixture was analyzed on a 10 ft by $^1/_8$ in. column of 3% SE-52 on 100-120 HP Chromosorb W with injection port at 150° and the oven temperature programmed as follows: 6 min at 145°, heated 9 min at 4°/min, heated 18 min at 2°/min (final temperature 220°), held at 220° for 20 min.

An 0.2-0.3-g sample of the reaction mixture was heated on a steam bath for 1.5 hr with 20 ml of 20% aqueous HCl and the organic layer was extracted with ether, neutralized, dried, and analyzed under the same conditions. The peak areas of 1,1-

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[11] (a) R. A. Sulzbach, *J. Organometal. Chem.*, **24**, 307 (1970); (b) A. J. Birch, E. G. Hutchinson, and G. S. Rao, *J. Chem. Soc. C*, 637 (1971).

[12] We are grateful to a referee for calling this to our attention.

[13] (a) D. Bryce-Smith, *J. Chem. Soc.*, 1603 (1956); (b) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964); (c) G. A. Russell and D. W. Lamson, *ibid.*, **91**, 3967 (1969); (d) S. Bank and J. F. Bank, *Tetrahedron Lett.*, 4533 (1969); (e) J. F. Garst, J. T. Barbas, and F. E. Barton, *J. Amer. Chem. Soc.*, **90**, 7159 (1968); (f) G. D. Sargent and G. A. Lux, *ibid.*, **90**, 7160 (1968); (g) J. F. Garst and J. T. Barbas, *Tetrahedron Lett.*, 3125 (1969); (h) J. F. Garst and F. E. Barton, *ibid.*, 587 (1969); (i) K. A. Bilevitch, N. N. Pubnov, and O. Yu. Okhlobystin, *ibid.*, 3465 (1968).

[14] H. F. Ebel and A. Luttringhaus, "Methoden der Organischen Chemie," Houben-Weyl, Ed., Georg Thieme Verlag, Stuttgart, 1970, p 498, and references cited therein.

[15] (a) A. G. Evans and J. C. Evans, *J. Chem. Soc. B*, 271 (1966). (b) As a referee has pointed out, the presence of meta-substituted products raises the possibility that a radical or radical-anion mechanism is contributing to product formation in those reactions involving alkyl iodides. We hope to gain further information on this question from the study mentioned here.

TABLE II

ANALYSIS OF THE ALKYLATION PRODUCTS FROM **2** AND ISOPROPYL HALIDES

				% rel peak area of							
				o-Ip			*p*-Ip		di-Ip		
Solvent	Alkali metal	X	IpX, mol	**4**	**5**	**3**	**4**	**5**	A	**7**	C
THF	Li	Cl	1	42	3	46	0	9			
THF	Li	Br	1	55	2	25	0	18			
THF	Li	I	1	46	2	22	2	28			
THF	Na	Cl	1	36	3	61	0	0			
THF	Na	Br	1	35	10	51	0	4			
THF	Na	I	1	48	1	38	2	11			
THF	K	Cl	1	0	0	98	2	0			
THF	K	Br	1	8	1	90	<1	0			
THF	K	I	1	15	2	63	18	2			
DEE	Na	Cl	1	4	12	60	4	8	2		10
DEE	Na	Br	1	3	11	68	2	10	1		5
DEE	Na	I	1	1	8	52	14	25			
THF	Li	Cl	2	57	0	34	1	8			
THF	Li	Br	2	56	1	25	15	3			
THF	Li	I	2	10	1	26	32	3	22	3	
THF	Na	Cl	2	36	3	61	0	0			
THF	Na	Br	2	20	1	64	9	4	2		
THF	Na	I	2	3	3	41	14	4	23	9	
THF	K	Cl	2	8	0	92	0				
THF	K	Br	2	6	0	93	1				
THF	K	I	2	0	0	68	19		11	2	
DEE	Li	Cl	2	23	1	46	0	30			
DEE	Li	Br	2	13	13	35	11	25	2		1
DEE	Li	I	2	8	0	41	18	28	4		1
DEE	Na	Cl	2	4	14	60	2	10	1		9
DEE	Na	Br	2	1	13	60	10	13			3
DEE	Na	I	2	1	7	46	3	42			1

diphenyl-2,2-dimethylethylene (from **3**) and **4** (*o*-Ip) were used to subdivide the appropriate peak in the first analysis into the relative areas due to **3** and **4** (*o*-Ip).

This analytical procedure was checked using known mixtures of **3**, **4** (*o*-Ip), and **4** (*p*-Ip). Results were found to be within the reproducibility of separate alkylation runs under identical reaction conditions. The peak areas quoted are reliable to ±10% for those products amounting to more than 10% of the reaction products.

Table II summarizes the analytical results obtained in the alkylation experiments. Small amounts of **1** (1–2%) and $Ph_2CHNHPh$ (2–8%) occurred in each experiment and these have been omitted from the analyses and the peak areas normalized.

Identification of Reaction Products.—Isolation and identification of **3** and **4** (*o*-Ip) have been reported.[2] The remaining compounds were initially identified by their vpc retention times and by "spiking" the reaction mixtures with reference compounds. Isolation of several products is reported below. The anils **5** (*o*-Ip), **5** (*p*-Ip), and **7** were further identified by acid hydrolysis of those reaction mixtures containing them and identification of the corresponding benzophenones by their vpc retention times. Reduction of the reaction mixtures with $LiAlH_4$ coupled with the observed increase in peak area of the corresponding substituted aniline provided further identification.

***N*-(*p*-Isopropylbenzhydryl)aniline (4, *p*-Ip).**—The crude reaction product (5.3 g) from a Li–THF–2IpI experiment (32% **4**, *p*-Ip) was heated on a steam bath for 2 hr with 35 ml of 20% HCl. The gummy solid which formed was filtered off and washed with ether to give a white solid, 0.78 g, mp 146–148°. A portion (0.28 g) was recrystallized from methanol–diethyl ether to give 0.11 g: mp 156–160°; ir (Nujol) identical with that of an authentic sample of the hydrochloride of **4** (*p*-Ip).

The remaining salt (0.50 g) was converted to the free amine with methanolic sodium hydroxide. Isolation of the amine by ether extraction gave 0.44 g of an oil whose ir spectrum (film) was identical with that of **4** (*p*-Ip).

***p*-Isopropylbenzophenone Anil (5, *p*-Ip).**—The reaction product from a Li–DEE–2IpBr reaction (25% **5**, *p*-Ip) was separated by preparative gas chromatography using a 20 ft by $^3/_8$ in. column containing 15% SE-30 on Chromosorb W operated at 275° with a flow rate of 150 ml/min of helium. The peak tentatively identified as **5** (*p*-Ip) was collected and found to have an ir (film) identical with that of an authentic sample.

Attempts to isolate the anil **5** (*p*-Ip) by column chromatography using CCl_4 as eluting agent resulted in partial hydrolysis. Only mixtures of **5** (*p*-Ip) and *p*-isopropylbenzophenone were isolated although the latter compound was obtained pure and identified by its ir.

***N*-(2,5-Diisopropylbenzhydryl)aniline (6).**—The crude reaction product (13.6 g) from a Li–THF–2IpI reaction (25% dialkylation) was dissolved in ether and the solution saturated with HCl. After filtering off the gummy solid which formed, the filtrate was washed with aqueous Na_2CO_3, dried, and evaporated. The residue (3.00 g) was chromatographed on 80 g of silica gel and eluted with CCl_4. The first material to elute (0.29 g) crystallized. Recrystallization from 80–100 petroleum ether gave 0.11 g: mp and mmp (with authentic **6**) 117–119°; nmr and ir (CCl_4) identical with those of **6**.

2,5-Diisopropylbenzophenone. Hydrolysis Product of 7.—The crude reaction product (2.8 g) from a Na–THF–2IpI experiment (32% dialkylation) was decomposed by heating with 20% aqueous HCl and the products were isolated by an ether extraction. After removal of the ether, the residue was dissolved in pentane and saturated with HCl. The solution was decanted from the gummy solid (0.23 g), washed with dilute Na_2CO_3 solution and water, dried, and evaporated (residue 2.02 g).

This residue was separated by preparative gas chromatography on a 10 ft by $^3/_8$ in. column packed with 3% SE-30 on 100–120 mesh Chromosorb W and operated at 190° with a He flow rate of 100 ml/min. Only the two largest peaks (of 6) were collected. The first peak proved to be 1,1-diphenyl-2-methylpropene on the basis of its ir and nmr spectrum. The second peak was contaminated with two minor impurities and was rechromatographed on a 20 ft by $^3/_8$ in. column containing 30% SE-30 on Chromosorb W using the same operating conditions. The main component was established as 2,5-diisopropylbenzophenone by comparison of its ir and nmr with reference spectra. One of the minor impurities proved to be *m*-isopropylbenzophenone on the basis of its ir spectrum.

Reaction of Benzophenone Anil with Isopropyllithium.—Isopropyllithium was prepared from isopropyl chloride in pentane and its concentration determined, as described by Applequist[16] (0.181 *M*).

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[16] D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **83**, 862 (1961).

A solution of 0.514 g (0.002 mol) of benzophenone anil in 30 ± 5 g of THF was cooled to −50° and treated with 11.0 ml (0.002 mol) of the prepared isopropyllithium. The solution immediately became deep orange red. After 15 min at −50°, the solution was allowed to warm to room temperature and stand overnight. The reaction product was isolated by dilution with water and extraction with ether.

In addition to the above experiment, three additional experiments were performed in which 0.002 mol of isopropyl chloride, bromide, and iodide were added to the benzophenone anil-isopropyl lithium reaction product as soon as it had warmed to room temperature. No color changes different from those described above were noted. The analysis of the products showed 15–20% of the benzophenone anil unreacted. The composition of the alkylation products was essentially constant in these four experiments and the average composition was 40 ± 4% of **3**, 23 ± 3% of **4** (*o*-Ip), 2 ± 1% of **5** (*o*-Ip), <1% of **4** (*p*-Ip), and 34 ± 1% of **5** (*p*-Ip).

Attempted Alkylation at the Nitrogen Anionic Center.—Following the procedure described earlier,[2a] the dianion **2** was treated with 1 equiv of *tert*-butyl alcohol and the resulting monoanion reacted with 2 equiv of isopropyl halide. Both isopropyl chloride and iodide were used with **2** (M = Li, Na, or *K*) in THF. The color changes observed and the absence of residual alkalinity in the final reaction mixture indicated that reaction had occurred. The crude products were examined by nmr for the presence of isopropyl groups but none were observed. Recrystallization of the product provided only *N*-benzhydrylaniline.

Reference Compounds.—*N*-Benzhydryl-*N*-isopropylaniline was prepared by stirring a solution of benzhydryl bromide (4.9 g, 0.02 mol) and *N*-isopropylaniline (5.9 g, 0.044 mol) in 15 ml of benzene and the solution stirred for 32 hr at 25°. After neutralizing, the mixture was distilled [bp 208–216° (15 mm)] and the distillate crystallized from 35–60° petroleum ether to give 3.3 g (55% yield) of solid: mp 91–92.5°; nmr (CCl_4) 0.95 and 1.17 (double d, J = 7 Hz, 6, CH_3), 3.60 (septet, 1, CH), 5.66 (s, 1, Ph_2CH), 6.2–7.5 (m, 15, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.65; H, 7.69; N, 4.69. Found: C, 87.47; H, 7.69; N, 4.68.

m-Bromoisopropylbenzene was prepared by refluxing a mixture of red phosphorus (62 g, 2 mol), 47% hydriodic acid (94 ml, 1 mol), and *m*-(bromophenyl)dimethylcarbinol[17] (71 g, 0.33 mol) with stirring for 40 hr. The mixture was cooled and filtered and the solid was washed with ether and water. From the combined filtrates, the ether phase was separated and washed with water, sodium bisulfite, and again with water. After drying and evaporating, the residue was distilled to give 54 g (84% yield) of *m*-bromoisopropylbenzene: bp 73° (2.5 mm); nmr (CCl_4) δ 1.15 (d, J = 7 Hz, 6, CH_3), 2.85 (septet, 1, CH), 7.0–7.4 (m, 4, aromatics).

m-Isopropylbenzoic acid was prepared by siphoning the Grignard reagent prepared from magnesium (6.04 g, 0.25 mol), *m*-bromoisopropylbenzene (50 g, 0.25 mol), and 300 ml of ether onto Dry Ice. After the slurry warmed to 25°, the mixture was acidified with aqueous HCl and the ether layer separated. The ether layer was extracted with aqueous NaOH and the aqueous extract was acidified with aqueous HCl. The yellow oil which separated crystallized giving 24.8 g (60% yield) of product: mp 42–45°; nmr (CCl_4) δ 1.34 (d, J = 7 Hz, 6, CH_3), 3.00 (septet, 1, CH), 7.3–8.1 (m, 4, aromatics).

This acid was converted to its acid chloride with thionyl chloride and the product distilled, bp 57–58° (0.3 mm).

Substituted Benzophenones.—The various substituted benzophenones were prepared by the procedure described by Friedman and Koca[18] using the appropriate aromatic hydrocarbon and acid chloride.

p-Isopropylbenzophenone (excess cumene + benzoyl chloride): 59% yield; bp 136–140° (0.5 mm) [lit.[19] 116–118° (0.04 mm); ir 1640 (C=O), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 1.29 (d, J = 7 Hz, 6, CH_3), 3.00 (septet, 1, CH), 7.0–8.0 (m, 9, aromatics); oxime mp 135–138° (lit.[20] 132°). The crude 2,4-dinitrophenylhydrazone (mp 160–182°) was chromatographed on alumina and the eluted derivative recrystallized from 1:7 ethyl acetate-ethanol, mp 194–196°.

Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99; N, 13.86. Found: C, 65.32; H, 5.17; N, 13.87.

The filtrate from the original preparation on evaporation gave material,[21] mp 125–131°. Recrystallization from ethyl acetate-ethanol gave an analytical sample, mp 136–139°.

Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99; N, 13.86. Found: C, 65.59; H, 5.11; N, 13.81.

m-Isopropylbenzophenone (excess benzene + *m*-isopropylbenzoyl chloride): 85% yield; bp 123–125° (0.5 mm); ir (film) 1655 (C=O), 1379 and 1358 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.20 (d, J = 6 Hz, 6, CH_3), 2.90 (septet, 1, CH), 7.0–7.5 (m, 9, aromatics); 2,4-dinitrophenylhydrazone mp 168–169.5.°

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.81; H, 7.19.

2,5-Diisopropylbenzophenone (excess *p*-diisopropylbenzene + benzoyl chloride): 50% yield; bp 146–150° (1 mm); ir (film), 1670 (C=O), 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.12 and 1.24 (double d, J = 3 Hz, 12, CH_3), 2.96 (m, 2, CH), 6.8–8.0 (m, 8, aromatics).

Substituted Benzophenone Anils.—The various substituted benzophenone anils were prepared from their corresponding substituted benzophenones and aniline by the procedure of Reddelien.[22]

p-Isopropylbenzophenone anil: 90% yield; bp 170–180° (1 mm); viscous yellow oil which crystallized. Recrystallization from 35–60° petroleum ether gave a 78% yield: mp 54–55°; ir (CCl_4) 1620 (C=N), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.15 and 1.28 (double d, J = 3 Hz, 6, CH_3), 2.85 (septet, 1, CH), 6.7–8.0 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{21}N$: C, 88.23; H, 7.07; N, 4.68. Found: C, 88.34; H, 7.21; N, 4.65.

m-Isopropylbenzophenone anil: 89% yield; viscous liquid; bp 167–169° (0.5 mm); ir (film) 1655 (C=N), 1378 and 1355 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.08 and 1.30 (double d, J = 6 Hz, 6, CH_3), 2.78 (septet, 1, CH), 6.4–8.0 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{21}N$: C, 88.23; H, 7.07; N, 4.68. Found: C, 88.00; H, 7.20; N, 4.79.

2,5-Diisopropylbenzophenone anil: 65% yield; bp 162–175° (0.3 mm), a very viscous orange liquid containing 5–10% unreacted ketone; ir (film) 1615 (C=N), 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 0.82 and 0.92 (double d, J = 6 Hz, 6, CH_3 of 2-Ip), 1.13 (d, J = 8 Hz, 6, CH_3 of 5-Ip), 2.67 (septet, 2, CH), 6.4–8.0 (m, 13, aromatics).

Substituted *N*-Benzhydrylanilines.—The various substituted *N*-benzhydrylanilines were prepared by a lithium aluminum hydride reduction of the corresponding substituted anils using the procedure previously described.[2b]

N-(*p*-isopropylbenzhydryl)aniline: 77% yield; viscous oil; bp 192–208° (0.6 mm) (hydrochloride mp 158–159°); ir (film) 3410 (NH), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) 1.18 (d, 6, J = 8 Hz, CH_3), 2.70 (septet, 1), 3.90 (broad s, 1, NH), 5.31 (s, 1, CH), 6.1–7.2 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.64; H, 7.69; N, 4.65. Found: C, 87.46; H, 7.89; N, 4.39.

The α-naphthylurea derivative had mp 130–130.5°.

N-(*m*-isopropylbenzhydryl)aniline: 81% yield; viscous yellow oil; bp 198° (2 mm); ir (film) 3410 (NH), 1397 and 1359 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.20 (d, J = 6 Hz, 6, CH_3), 2.85 (septet, 1, $(CH_3)_2CH$), 3.90 (broad s, 1, NH), 5.40 (s, 1, CH), 6.3–7.4 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.64; H, 7.69; N, 4.65. Found: C, 87.97; H, 7.84; N, 4.69.

N-(2,5-Diisopropylbenzhydryl)aniline: 55% yield; mp 111–114°. Three recrystallizations from 80–100° petroleum ether provided an analytical sample: mp 119–120.5°; ir (CCl_4) 3450 (NH), 1385 and 1365 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 1.0–1.4 (m, 12, CH_3), 2.6–3.4 (m, 2, CH), 4.10 (broad s, 1, NH), 5.80 (s, 1, CH), 6.4–7.5 (m, 13, aromatics).

Anal. Calcd for $C_{25}H_{29}N$: C, 87.42; H, 8.51; N, 4.08. Found: C, 87.38; H, 8.82; N, 4.21.

Registry No.—**1**, 574-45-8; **2**, 32388-60-6; **4** (*p*-Ip), 23431-27-8; **4** (*p*-Ip) α-naphthylurea derivative, 32388-77-5; **4** (*p*-Ip) HCl, 32388-79-7; **5** (*p*-Ip),

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[17] M. Stiles and A. Sisti, *J. Org. Chem.*, **25**, 1691 (1960); 84% yield, bp 100° (3 mm).

[18] L. Friedman and R. Koca, *ibid.*, **33**, 1255 (1968).

[19] W. E. Bachmann, E. Carlson, and J. C. Moran, *ibid.*, **13**, 916 (1968).

[20] A. W. Smith, *Chem. Ber.*, **24**, 4025 (1891).

[21] Syn-anti isomers from substituted benzophenones have been observed: see, for example, P. A. S. Smith and E. P. Antoniades, *Tetrahedron*, **9**, 210 (1960).

[22] G. Reddelien, *Chem. Ber.*, **46**, 2718 (1913).

18864-77-2; **5** (*o*-Ip), 19103-10-7; **6**, 32414-35-0; **7**, 32388-64-0; Li, 7439-93-2; Na, 7440-23-5; K, 7440-09-7; isopropyl chloride, 75-29-6; isopropyl bromide, 75-26-3; isopropyl iodide, 75-30-9; *N*-benzhydryl-*N*-isopropylaniline, 32388-68-4; *m*-bromoisopropylbenzene, 5433-01-2; *m*-isopropylbenzoic acid, 5651-47-8; *p*-isopropylbenzophenone, 18864-76-1, 32388-72-0 (2,4-DNPH); *m*-isopropylbenzophenone, 32388-73-1; 2,5-diisopropylbenzophenone, 2887-73-2; *m*-isopropylbenzophenone anil, 32388-75-3; 2,5-diisopropylbenzophenone anil, 32388-64-0; *N*-(*m*-isopropylbenzhydryl)aniline, 32388-78-6.

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Notes

Reactions of Some Dithiazolium Cations with Potassium Cyanate

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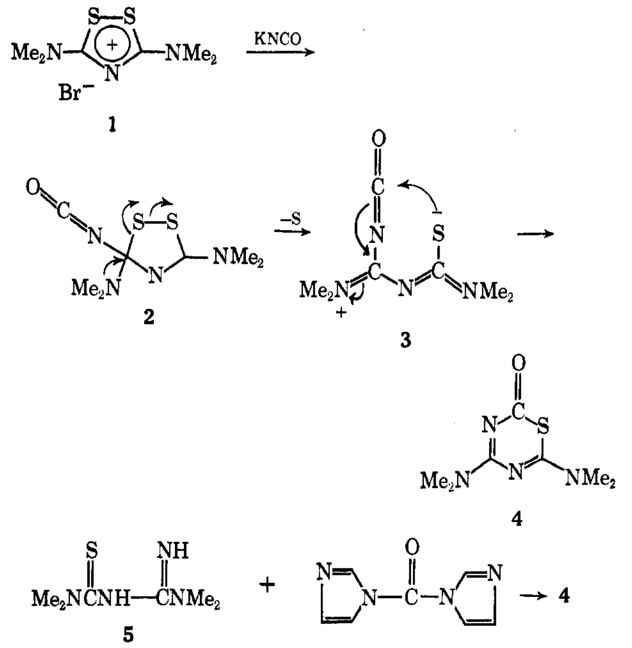
In the course of our studies of 3,5-disubstituted 1,2,4-dithiazolium salts as insect chemosterilants,[1] we recently found that 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (**1**) and several related dithiazolium salts react with sodium azide in DMF or DMSO to provide 3,5-disubstituted 1,2,4-thiadiazoles.[2] Cyanate ion, like azide, is a nucleophile that contains a potential electrophilic center, and we felt that, if ring opening of **1** could be initiated by KNCO, a reaction similiar to the NaN_3 addition should occur except that in this case a six-membered ring would result. Indeed, when **1** and KNCO were allowed to react in refluxing DMF, a neutral compound was obtained (71%) that has been identified by its elemental analysis, ir, nmr, and mass spectra as 4,6-bis(dimethylamino)-2*H*-1,3,5-thiadiazin-2-one (**4**). Final confirmation of structure came from an alternate synthesis achieved by condensing 3-(*N*,*N*-dimethylamidino)-1,1-dimethyl-2-thiourea[1,2] (**5**) with carbonyldiimidazole in refluxing toluene (Scheme I).

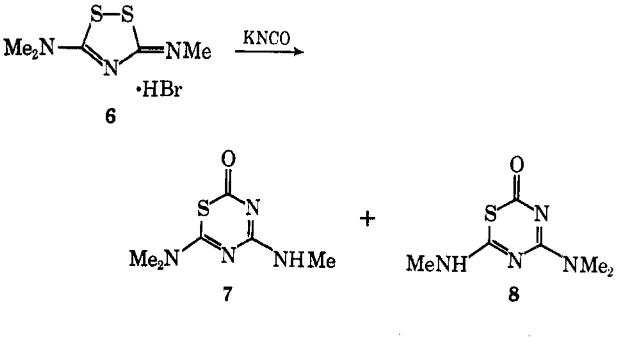
The nmr signals of the methyl hydrogens of dimethylamides and related compounds are frequently observed as doublets because of restricted rotation around the N–C bonds.[3] Both of the dimethylamino signals of **7** appear as doublets at room temperature (coalescence temperatures in chlorobenzene *ca.* 45 and 87°). This constitutes an interesting extension of the dialkylamide phenomenon, as in this case the carbonyl group is in a heterocyclic ring. We assume, without evidence, that the 4-dimethylamino group has the larger rotation barrier.

Scheme I



3,5-Dipiperidino- and 3,5-bis(1-pyrrolidinyl)-1,2,4-dithiazolium bromides reacted analogously with KNCO to give 4,6-dipiperidino- and 4,6-bis(1-pyrrolidinyl)-2*H*-1,3,5-thiadiazin-2-ones in 40–88% yield (few attempts were made to optimize conditions or yields). Thus it appears that this constitutes a general synthesis of 4,6-bis(dialkylamino)-1,3,5-thiadiazin-2-ones, a previously unreported class of compounds.

5-(Dimethylamino)-3-(methylimino)-3*H*-1,2,4-dithiazole hydrobromide (**6**) reacted with NaN_3 to give 5-



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[1] J. E. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Borkovec, *J. Med. Chem.*, in press.

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[3] W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).