

$\text{BrCF}_2\text{C}(=\text{O})\text{Br}$ , with the molecular ion at 236 ( $\text{C}_2\text{Br}_2\text{F}_2\text{O}$ ) and the most abundant  $m/e$  at 129 ( $\text{CF}_2\text{Br}^+$ ). The properties of the ethyl ester of  $\text{BrCF}_2\text{C}(=\text{O})\text{Br}$  were identical with a sample of authentic  $\text{BrCF}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_3$  prepared from the corresponding acid and ethanol.<sup>5</sup>

Dibromodifluoromethane was identified mass spectrally with a molecular ion ( $\text{CF}_2\text{Br}_2$ ) at 208 and the most intense  $m/e$  at 191 ( $\text{CFBr}_2^+$ ).

Carbon dioxide and carbon monoxide were identified mass spectrally when the decomposition was performed in such a way as to intercept the effluent gases from the thermolysis by an AEI mass spectrometer.

**Registry No.**—Bromodifluoroacetic anhydride, 7601-98-1.

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(5) G. A. Grindahl, W. X. Bajzer, and O. R. Pierce, *J. Org. Chem.*, **32**, 603 (1967).

## O vs. C Alkylation of Ethyl Acetoacetate

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Following a number of isolated instances of O alkylation of ethyl acetoacetate,<sup>1</sup> several reports of the fairly general applicability of this reaction have appeared by now.<sup>2-4</sup> These studies have revealed that the O/C-alkylation ratio is remarkably dependent on the structure of the alkyl group, the solvent, the temperature and the cation; however, a more detailed investigation of these effects was hampered by the fact that the over-all yields are often rather poor. A recent communication concerning this reaction in hexamethylphosphoramide<sup>5</sup> (HMPA) prompts us to report our own results obtained with this solvent. We have found that the use of HMPA allows not only better yields, but also the highest O/C ratios yet observed. This reaction is therefore useful for studies of ambident anion behavior as well as for synthetic purposes. The alkylation of ethyl acetoacetate is described in Scheme I.

In most cases, the reaction was carried out at about 100°; the anion was generated by the addition of ethyl acetoacetate to an ethoxide salt followed by the careful removal of ethanol, and the dissolution of the remaining solid in HMPA. The alkylating agent was in each case injected slowly under the surface of the solution so as to minimize evaporation losses. The products could be readily separated from the starting material, the solvent

(1) (a) G. D. Lander, *J. Chem. Soc.*, 729 (1900); (b) J. L. Simonsen and R. Storey, *ibid.*, 2106 (1909); (c) C. D. Hurd and K. Wilkinson, *J. Amer. Chem. Soc.*, **70**, 739 (1948); (d) S. J. Rhoads, R. W. Hasbrouck, C. Pryde, and R. W. Holder, *Tetrahedron Lett.*, 669 (1963); (e) K. R. Brower, R. L. Ernst, and J. S. Chen, *J. Phys. Chem.*, **68**, 3814 (1964).

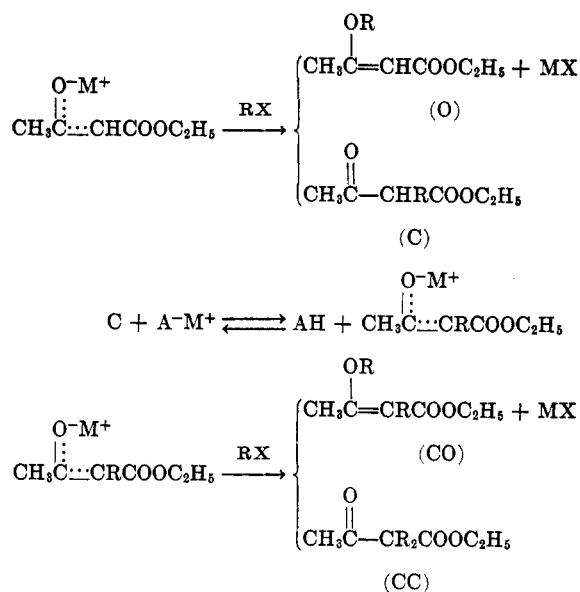
(2) S. T. Yoffe, K. V. Vatsuro, E. E. Kugutcheva, and M. I. Kabachnik, *Tetrahedron Lett.*, 593 (1965).

(3) G. Brieger and W. M. Pelletier, *ibid.*, 3555 (1965).

(4) W. J. le Noble and J. E. Puerta, *ibid.*, 1087 (1966).

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SCHEME I



and added water by means of extractions with *n*-pentane. The analysis of the four products could be carried out completely by means of either vpc or nmr, as detailed in the Experimental Section. The two methods agreed closely in each instance. Table I shows some of the results of the alkylation of the potassium salt of ethyl acetoacetate in HMPA. The reason for the improved yields is not known; however, alkylation and reduction of DMSO by alkylating agents are known reactions.<sup>6</sup> Of equal interest is the fact that the O/C ratios are a great deal higher in HMPA. This ratio increases along the series acetone < acetonitrile < DMSO  $\approx$  dimethylformamide (DMF)  $\approx$  dimethylacetamide  $\approx$  N-methylpyrrolidone < HMPA (data in part from ref 3). A similar sequence (tetrahydrofuran (THF) < ethylene glycol dimethyl ether (glyme) < DMSO  $\approx$  DMF) has been observed<sup>7</sup> in several alkylation reactions of sodium  $\beta$ -naphthoxide. It has been pointed out that the dielectric constants (in parentheses) of these solvents increase roughly in the same order: THF (7)  $\approx$  glyme (7) < DMSO (45)  $\approx$  DMF (37), and acetone (21) < acetonitrile (39)  $\approx$  dimethylacetamide (37). However, the dielectric constant of HMPA is only equal to 30.<sup>8</sup> It is furthermore observed<sup>3,4</sup> that a rise in temperature causes an increase in O/C ratio although the dielectric constant rapidly declines with increasing temperature; we therefore prefer to think of these trends as a correlation with solvent basicity. Such basicity can be defined and measured in a number of ways. One of these is the downfield shift in parts per million of the proton signal of chloroform in infinite dilution in the solvent of interest, as compared to that in cyclohexane. This measure is used here because most of the appropriate data are available: THF, 0.80; acetone, 0.94; DMF, 1.30; DMSO, 1.34; HMPA, 2.03. To the limited extent then that data involving aprotic solvents are available, the O/C ratio appears to correlate

(6) For a recent review of the properties of DMSO, see D. Martin, A. Weise, and H. J. Niclas, *Angew. Chem. Intern. Ed. Engl.*, **6**, 318 (1967).

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

(8) For an up-to-date review of the properties of HMPA, see H. Normant, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1046 (1967).

TABLE I  
COMPARISON OF YIELDS AND PRODUCT RATIOS IN HMPA AND DMSO

Alkyl halide	Yield <sup>a,c</sup>	Mole ratio of the products			
		O	C	CC	CO
Isopropyl chloride	78 (52)	81 (62)	19 (38)	0 (0)	0 (0)
<i>n</i> -Propyl chloride	89 (73)	61 (47)	23 (25)	8 (28)	8 (0)
Ethyl bromide	94 (73)	46 (26)	34 (68)	16 (6)	4 (0)
Methyl iodide <sup>b</sup>	83 (74)	14 (4)	58 (79)	28 (17)	0 (0)
Allyl chloride	88 (80)	17 (0)	45 (100)	38 (0)	0 (0)
Benzyl chloride	93 (60)	13 (5)	51 (45)	36 (50)	0 (0)

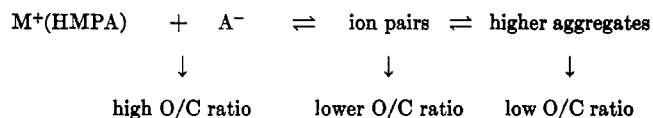
<sup>a</sup> Percentage of the alkylating agent accounted for by the products. <sup>b</sup> The sodium salt was used in this case; the potassium salt in all others. <sup>c</sup> The data in parentheses are taken from our earlier study with DMSO.<sup>4</sup>

better with basicity than with the dielectric constant. This question has been discussed by Delpuech<sup>9</sup> in another connection.

It is of interest to compare our results with earlier studies of medium effects on ambident anion behavior.<sup>7,10,11</sup> These studies show that the use of more highly basic aprotic solvents will tend to solvate the counterion and hence leave the oxygen atom of the anion exposed to approach by the alkylating agent; less basic solvents will lead to extensive ion pairing or even clustering, and in such cases C alkylation becomes the alternative mode of alkylation. The effect of heterogeneity<sup>10</sup> in certain cases may well have a similar basis; one may visualize the oxygen atom of phenoxide ion as protected by several counterions in the solid phase, but perhaps by only one ion in benzene solution, and thus account for C alkylation in the former case and O alkylation in the latter. In protic solvents, on the other hand, dissociation may be complete, but now the oxygen atom of the anion is shielded by several solvent molecules, and a lowered O/C ratio again results; this has been shown<sup>11</sup> by the correlation of O/C ratios with H bonding ability. These effects can be summarized by the statement: *the freer the anion, the larger the O/C ratio.*

In HMPA the O atom of the ambident anion may well be more accessible than in any other known medium. This is supported by the data shown in Table II. The O/C ratio does not change as the cation is varied in size from Na<sup>+</sup> to NBu<sub>4</sub><sup>+</sup>, nor does a reagent such as tetraglyme have any effect; the smallest cation, Li<sup>+</sup>, depresses the ratio somewhat. Reutov<sup>5</sup> found such a depression with both lithium and sodium with the use

of diethyl sulfate at 20°. We also find, as he did, that the reaction with the lithium salt is much slower. In contrast, small cations tend to depress the O/C ratio to a considerable degree in DMSO,<sup>3,4</sup> and such cation effects have also been noted in the alkylations of other ambident anions.<sup>12,13</sup> Furthermore, although it is observed that the O/C ratio in DMSO tends to increase with increasing temperature,<sup>3,4</sup> as would be expected if further dissociation of ion pairs occurs as the temperature is increased, our studies show no such temperature dependence in HMPA. With isopropyl chloride and the potassium salt, the O/C ratio was 81/19 at 50, 90 and 130°. It is, of course, not necessary that the entire salt sample be completely dissociated in HMPA, as long as the ion association-dissociation equilibria are rapid.



The low sensitivity of the O/C ratio to either cation or temperature changes suggests that the alkylation in HMPA proceeds largely through the free anion. It is of interest to point out in this connection that conductance measurements have recently shown several types of ion pairs to be completely unassociated<sup>14</sup> in dilute HMPA solution. It therefore seems possible that the O/C ratio is reaching a maximum in HMPA, and that we are in fact observing the limiting value;<sup>15</sup> any protic or less basic medium would lower the ratio through selective deactivation of the oxygen site by either one or more counterions, or by one or more solvent molecules.

Not a great deal is known as yet about the influence of the alkyl group on the O/C ratio. It is commonly assumed that the ratio is increased as the S<sub>N</sub>1 character of the alkylating agent increases,<sup>16</sup> since such a correlation allows a ready interpretation of the effect of silver ion on the course of many alkylation reactions. In the case of ethyl acetoacetate, the facts that diazomethane<sup>17</sup>

TABLE II

O/C RATIO WITH ALLYL CHLORIDE AT 95°  
IN HMPA WITH VARIOUS CATIONS

Cation	O/C	Reactions time, min
Li <sup>+</sup>	12/88	210
Na <sup>+</sup>	17/83	5
K <sup>+</sup>	17/83	3
N-( <i>n</i> -Bu) <sub>4</sub> <sup>+</sup>	17/83	3
K <sup>+</sup> (tetraglyme) <sup>a</sup>	16/84	3

<sup>a</sup> Highly effective in separating ion pairs [see T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **89**, 2764 (1967)], and thus in promoting O alkylation [see H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org., Chem.*, **33**, 2222 (1968)].

(9) J. J. Delpuech, *Tetrahedron Lett.*, 2111 (1965).

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

(11) N. Kornblum, P. J. Berrigan, and W. J. le Noble, *ibid.*, **85**, 1141 (1963).

(12) R. Gompper, *Angew. Chem. Intern. Ed. Engl.*, **3**, 560 (1964).

(13) (a) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Amer. Chem. Soc.*, **80**, 1391 (1958); (b) I. Forsblad, *Arkiv Kemi*, **14**, 403 (1960); (c) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **84**, 43 (1962).

(14) (a) A. Cserhegyi, J. Chaudhuri, E. Franta, J. Jagur-Grodzinski, and M. Szwarc, *ibid.*, **89**, 7129 (1967); (b) H. F. Ebel and R. Schneider, *Angew. Chem. Intern. Ed. Engl.*, **4**, 878 (1965).

(15) For another interesting example of this phenomenon, see S. G. Smith and D. V. Milligan, *J. Amer. Chem. Soc.*, **90**, 2393 (1968).

(16) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955).

(17) F. G. Arndt in "Organic Analysis," Vol. I, Interscience Publishers, New York, N. Y., 1953, pp 197-241.

TABLE III  
EFFECTS OF STERIC AND ELECTRONIC FACTORS ON THE O/C RATIO IN HMPA

No.	Chloride <sup>a,c</sup>	Yield, %	Product ratio, %			
			O	C	CC	CO
1	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	89	61	23	4	4
2	(CH <sub>3</sub> ) <sub>2</sub> CH-	78	81	19	0	0
3	CH <sub>2</sub> CH <sub>2</sub> (CH <sub>3</sub> )CH-	75	86	14	0	0
4	(CH <sub>3</sub> ) <sub>2</sub> CCH <sub>2</sub> -	13 <sup>b</sup>	100	0	0	0
5	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	93	13	51	36	0
6	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH-	93	39	61	0	0
7	2,6-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> -	93	19	81	0	0
8	4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	88	11	57	32	0
9	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	97	13	54	33	0
10	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	95	11	48	41	0
11	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -	97	9	50	41	0

<sup>a</sup> The temperature was approximately 100°; in each case potassium was used. <sup>b</sup> This reaction was stopped at low conversion because of the onset of side reactions (ester ether interchange reactions; see Experimental Section). <sup>c</sup> Registry no.: 3 (C derivative) 1540-31-4; 3 (O derivative), 1540-22-3; 4 (O derivative), 19289-27-1; 6 (C derivative), 19289-28-2; 6 (O derivative), 19289-29-3; 7 (C derivative), 19289-30-6; 7 (O derivative), 19289-31-7.

and chloromethyl methyl ether<sup>1b</sup> give ample amounts of the enol ethers have been considered to substantiate that view. However, 2-nitropropane is O alkylated by 3-bromocyclohexene but C alkylated by tropylium bromide;<sup>18</sup> ethyl acetoacetate and tropylium bromide in unbuffered aqueous solution give the C-tropyl derivative.<sup>19</sup> Additional examples are quoted in the preliminary report.<sup>4</sup> In that report it was demonstrated that, in the reaction of a series of common halides with ethyl acetoacetate anion, the O/C ratio in DMSO was highest for those alkylating agents having the lowest S<sub>N</sub>2 reactivity, and that S<sub>N</sub>1 reactivity did not appear to correlate with it. Similar results are apparent from an inspection of Table I.<sup>20</sup>

S<sub>N</sub>2 reactivity is usually associated with steric effects, whereas S<sub>N</sub>1 reactivity is governed primarily by electronic factors. Our data in HMPA (Table III) show that steric effects are more important in this reaction. Within each series the effect of crowding near the halogen-bonded carbon atom is an increase in the O/C ratio; thus, neopentyl chloride leads to exclusive O alkylation. This effect has also been observed in the alkylation of cyclic β-keto esters by α-halo esters,<sup>21</sup> and in the alkylation of enolates (Table II, footnote a). On the other hand, variation of the *para* substituent in benzyl chloride from methoxy to trifluoromethyl has no significant effect. The steric factor cannot be considered exclusively responsible, however. Certainly the steric requirements of allyl and *n*-propyl chloride are not very different, to mention an obvious example.

The effect is probably related to the fact that acetyl oxygen can be easily approached from almost any direction, but the α-carbon atom can of course only be approached in a direction perpendicular to the plane containing its three bonds. Alkylating agents that are

rather highly branched near the site of the leaving group would therefore prefer the oxygen atom more than those that are not so crowded.

The leaving group effect<sup>3,4,22</sup> also appears to fit the S<sub>N</sub>2 reactivity correlation, but this cannot be explained by the same steric argument. Perhaps the most reasonable explanation of this observation is due to Pearson and Songstad,<sup>23</sup> who attribute it to symbiosis, the tendency of either hard or soft ligands to flock together at the site of displacement.

#### Experimental Section

**Alkylations.**—A typical example follows. About 0.1 mol of the alkali metal is dissolved in ethanol under nitrogen in a three-necked flask fitted with a gas inlet, a reflux condenser capped with a drying tube, a thermometer well and a magnetic stirrer. An equivalent amount of ethyl acetoacetate is added and the alcohol is removed by flash evaporation. The residue is vacuum dried for several hours, and dissolved with stirring in 200 ml of HMPA; meanwhile the mixture is heated to 95–125°. The nitrogen inlet is replaced by a serum cap. The equivalent amount of alkyl halide is introduced below the surface of the solution by means of a syringe fitted with a long needle. The syringe also permits the withdrawal of small samples, which can be titrated to monitor the remaining base. When the reaction is over, the mixture is cooled, poured into 500 ml of cold water, neutralized if necessary and extracted with several 100-ml portions of pentane which are combined, washed with a little water to remove traces of ethyl acetoacetate and HMPA, briefly dried over anhydrous magnesium sulfate and flash evaporated. The crude product can be analyzed by either nmr or vpc techniques. Nmr analysis depends on the facts that the O derivative has a vinyl proton signal at τ 4.8–5.15 and that the acetyl methyl protons of the O, C, and CC derivatives are invariably well separated (τ 7.6–7.7, 7.8–7.95 and 7.8–8.15, respectively). For vpc analysis in the aliphatic series, a 1.75-m column charged with 20% Apiezon L absorbed on 20/80 Chromosorb W was used at 130–155°. For the aromatic compounds, a 5-ft column charged with 3% OV-17 absorbed on 100/120 Airopak 30 was used at 175–195°. The retention times for ethyl acetoacetate and the O, C, CC, and CO derivatives would typically be in the ratio 1:2:3:5:8. Analytical data and physical properties of the products are shown in Table IV. Since Reutov<sup>5</sup> has reported that the presence of an equivalent of alcohol may affect the product ratio, we point out that we treated the sodium salt with benzene in order to remove any trace of alcohol by means of azeotropic distillation; this did not affect the product distribution. *Anal.* Calcd for C<sub>6</sub>H<sub>9</sub>O<sub>2</sub>Na: Na, 15.1. Found: Na, 15.5.

The experiment involving the NBu<sub>4</sub><sup>+</sup> salt was carried out by

(22) (a) R. Chong and P. S. Clezy, *ibid.*, 741 (1966); (b) G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, 51 (1966).

(23) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(18) M. Bersohn, *J. Amer. Chem. Soc.*, **83**, 2136 (1961).

(19) M. E. Vol'pin, I. S. Akhrem, and D. N. Kursanov, *J. Gen. Chem., USSR* **30**, 1207 (1960); see also K. Conrow, *J. Amer. Chem. Soc.*, **81**, 5461 (1959).

(20) (a) The reaction of allyl chloride is of interest in that no O derivative was obtained in DMSO at all. The reaction in HMPA with the bromide has been examined by Normant and Cuvigny,<sup>20b</sup> who apparently did not find any of the enol ether in that case either. (b) H. Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, 1881 (1965).

(21) A. Chatterjee, D. Banerjee, and S. Banerjee, *Tetrahedron Lett.*, 3851 (1965).

TABLE IV  
 ANALYTICAL DATA<sup>a</sup> AND PHYSICAL PROPERTIES<sup>b</sup> OF THE ALKYLATION PRODUCTS<sup>c</sup>

Alkyl group	C derivative		O derivative		CC derivative	
	$n_D^{20}$ or mp, °C	H, %	$n_D^{20}$ or mp, °C	H, %	$n_D^{20}$ or mp, °C	H, %
CH <sub>3</sub>	1.4195 <sup>d</sup>		1.4480		1.4165	
	(1.4194) <sup>d-f</sup>		(1.4479) <sup>f</sup>		(1.4162) <sup>g,j</sup>	
C <sub>2</sub> H <sub>5</sub> <sup>e</sup>	1.4212		30.0		1.4299	
	(1.4225) <sup>d-f</sup>		(30.2) <sup>g,j</sup>		(1.4305) <sup>d-f</sup>	
n-C <sub>3</sub> H <sub>7</sub> <sup>e</sup>	1.4271		1.4498	9.28 <sup>f</sup>	1.4356	
	(1.4255) <sup>d-f</sup>		(1.4496) <sup>f</sup>	(9.36)	(1.4369) <sup>f</sup>	
i-C <sub>3</sub> H <sub>7</sub>	1.4250 <sup>d</sup>		1.4496	9.13 <sup>f</sup>		
	(1.4252) <sup>d,f,h</sup>		(1.4496) <sup>f,h</sup>	(9.36)		
sec-C <sub>4</sub> H <sub>9</sub>	1.4290	64.20	1.4486	9.69		
		(64.49)		(9.74)		
neo-C <sub>4</sub> H <sub>9</sub> <sup>i</sup>			1.4456	9.95		
				(10.07)		
CH <sub>2</sub> =CHCH <sub>2</sub>	1.4362		1.4582 <sup>i</sup>		1.4547	
	(1.4365) <sup>k</sup>				(1.4572) <sup>l</sup>	
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	1.4989		1.5225	7.39 <sup>f</sup>	1.5427	
	(1.4988) <sup>f,m</sup>		(1.5222) <sup>f</sup>	(7.32)	(1.5430) <sup>m</sup>	
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH	85.5	76.91	1.5621	6.48		
		(77.00)		(6.80)		
2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	1.5060	72.17	68	8.25		
		(72.55)		(8.12)		
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	1.5062 <sup>d</sup>	66.94	1.5391 <sup>d</sup>	7.08	1.5340 <sup>d,n</sup>	
	(1.5077) <sup>o</sup>	(67.20)		(7.20)		
4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	1.5020	72.08	1.5241	7.49	49	77.74
		(71.77)		(7.74)		(78.08)
4-C(C <sub>6</sub> H <sub>4</sub> )CH <sub>2</sub> <sup>p</sup>	1.5119	61.50	1.5372	5.87	92.5	63.28
		(61.30)		(5.94)		(63.34)
4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> <sup>q</sup>	1.4590	57.93		5.23	65	58.97
		(58.33)		(5.25)		(59.19)

<sup>a</sup> Theoretical values are shown in parentheses. <sup>b</sup> Literature values are shown in parentheses. <sup>c</sup> The small amounts of CO derivatives obtained with C<sub>2</sub>H<sub>5</sub> and n-C<sub>3</sub>H<sub>7</sub> were identified by means of nmr only. <sup>d</sup> At 20°. <sup>e</sup> C. M. French, *Trans. Faraday Soc.*, **48**, 216 (1952). <sup>f</sup> Reference 4. <sup>g</sup> D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960). <sup>h</sup> Reference 2. <sup>i</sup> When the reaction is continued beyond 13% conversion, side reactions set in giving rise to products with ethyl ether and neopentyl ester linkages. Eventually all four cross-products are obtained. They were isolated by vpc and identified by nmr (*Anal.*). Calcd for neopentyl β-ethoxycrotonate: C, 65.97; H, 10.07. Found: C, 65.70; H, 9.87. *Anal.* Calcd for neopentyl β-neopentoxycrotonate: C, 69.38; H, 10.81. Found: C, 68.97; H, 10.38. <sup>j</sup> W. M. Lauer and E. I. Kilburn, *J. Amer. Chem. Soc.*, **59**, 2586 (1937). <sup>k</sup> M. S. Schechter, N. Green, and F. B. LaForge, *ibid.*, **71**, 3165 (1949). <sup>l</sup> At 17.4°. <sup>m</sup> J. W. Bruhl, *J. Prakt. Chem.*, **50**, 132, 137 (1894). <sup>n</sup> H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961). <sup>o</sup> This value may not be that of the pure compound since the product was not obtained in analytically pure form. Treatment with aqueous base gave rise to di-p-methoxybenzylacetic acid [mp 105° (*Anal.*). Calcd: H, 6.67; neut equiv, 300. Found: H, 6.73; neut equiv, 289] for which the C analysis was also outside the normally acceptable limits. <sup>p</sup> At 17.2°. <sup>q</sup> V. V. Feofilaktov, *Bull. Acad. Sci. USSR, Classe Sci. Chim.*, **521** (1941); *cf. Chem. Abstr.*, **37**, 23482 (1943). <sup>r</sup> Further data: O derivative, Cl, 13.61 (calcd 13.92); C derivative, Cl, 14.47 (calcd 13.92); CC derivative, Cl, 18.74 (calcd 18.69). <sup>s</sup> The O derivative decomposed on standing and could not be analyzed other than by nmr. Most of the substituted benzyl derivatives required tlc for final purification.

the addition of 1 equiv of tetra-*n*-butylammonium chloride and the precipitation of the potassium chloride before injecting the alkylating agent. The experiment involving tetraglyme was carried out by the addition of 1 equiv of tetraglyme purified by distillation from calcium hydride.

**Materials.**—The solvent can be readily recovered from the alkylation mixtures in about 80% yield as follows. The water is removed by flask evaporation for about 8 hr at 35–40°; the remaining liquid is dried overnight over magnesium sulfate and finally vacuum distilled from calcium hydride at 76–80° (1 mm),  $n_D^{25}$  1.4570 (lit.<sup>24</sup> 1.4570). *p*-Trifluoromethylbenzoyl chloride was converted into the ethyl ester by the procedure of Hass and Bender.<sup>25</sup> The product was reduced to the benzyl alcohol<sup>25</sup> by the method of Nystrom and Brown.<sup>26</sup> The alcohol was then converted<sup>27</sup> into the chloride.<sup>28</sup> *p*-Methoxybenzyl chloride<sup>29</sup> was prepared similarly. 2,6-Dimethylbenzyl chloride was prepared from the corresponding benzoic acid as reported by Raaen and Eastham.<sup>30</sup> The physical constants of these compounds agreed in all cases closely with those reported by the authors quoted.

**Registry No.**—Ethyl acetoacetate, 141-97-9.

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### Reduction of Ferrocene Methiodides. Synthesis of the Dimethylferrocenes

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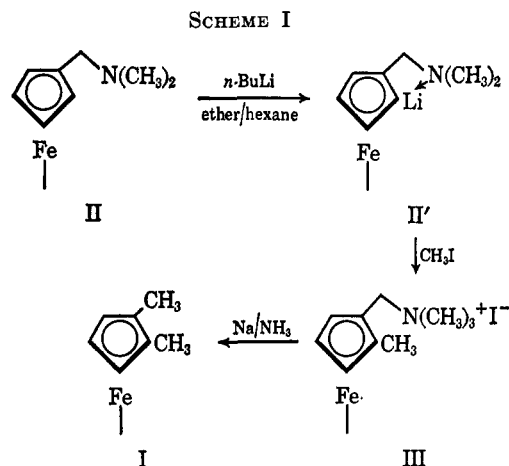
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We have recently described a method which is suitable for the preparation of alkylferrocenes.<sup>2</sup> Utilizing this method, as well as another reduction procedure, we have succeeded in an unequivocal synthesis of 1,2-dimethylferrocene (I). This method constitutes the first direct preparation of 1,2-dimethylferrocene. Syntheses of this compound from 1,2-disubstituted precursors have been reported recently.<sup>3</sup>

Dimethylaminomethylferrocene (II) was lithiated with *n*-butyllithium yielding the 2-lithio intermediate II'.<sup>4</sup> Treatment of this intermediate with a large excess of methyl iodide and reprecipitation of the crude product from methanol/ether yielded 2-methyl-*N,N,N,N*-trimethylferrocenylmethylammonium iodide (III). The crude methiodide was taken directly to the reduction step as described for methylferrocene.<sup>2</sup> Work-up

and chromatography on neutral alumina brought a 78% yield of 1,2-dimethylferrocene. Scheme I outlines this procedure.



The purity of the 1,2-dimethylferrocene was monitored by vapor phase chromatography (vpc) on a 6-ft Apiezon L (15%) on Chromosorb P column. Repeated chromatograms demonstrated conclusively that material of from 98 to 99% purity could be obtained by this method. The major impurities were methylferrocene (identical retention time as that of an authentic sample) and an unidentified material which had a longer retention time than I. Methylferrocene was probably formed by reduction of the methiodide of unmethylated amine.

Attempts to improve the purity of I by column chromatography on alumina or by recrystallization proved discouraging. However, several fractional reprecipitations of the crude methiodide from methanol/ether gave methiodide which decomposed between 178 and 179° to a black powder. An nmr spectrum of methiodide III in  $\text{CDCl}_3$  exhibited a two-proton singlet at 4.78 ppm assigned to the methylene protons, a one-proton signal at 4.55 ppm assigned to the ring proton adjacent to the trimethylaminomethyl substituent, a seven-proton signal at 4.23 ppm assigned to the remaining ring protons, and a nine- and a three-proton signal at 3.23 and 2.17 ppm, respectively, assigned to the nitrogen and ring methyl groups. This purified methiodide (III) upon reduction and work-up yielded 1,2-dimethylferrocene of purity greater than 99% by vpc. 1,2-Dimethylferrocene has the following properties: parent peak at  $m/e$  214; bp 67–68° (0.5 mm); mp 33–35°. An nmr spectrum in  $\text{CDCl}_3$  showed six protons at 1.91 ppm and eight protons at 3.98 ppm. An infrared (ir) spectrum exhibited bands at 9.04 and 9.98  $\mu$ .<sup>5</sup>

A somewhat different route was also found to produce 1,2-dimethylferrocene. Lithiation of dimethylaminomethylferrocene and treatment with methyl iodide was effected essentially as recorded above. The methiodide thus formed was isolated and purified. Reduction of this purified methiodide by an overnight treatment with lithium aluminum hydride in tetrahydrofuran (THF) gave I in 56% yield.

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