methylene chloride. The combined extract was dried over anhydrous sodium sulfate, concentrated, and chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (3:1) to afford 72.7 mg (75%) of pure pyridone **6**, mp 185–187 °C. This sample was identical in all respects with the sample isolated from method A.

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Registry No.—**3**, 42772-88-3; **3**-*3*-d_1, 63449-27-4; **3**-*3,6,6'*-d_3, 63449-28-5; **5**, 42772-86-1; **6**, 63449-29-6; **6**-*1,3,6'*-d_3, 63449-30-9; **7**, 49669-19-4; **8**, 63449-31-0; bis(6-bromo-2-pyridyl) ketone, 42772-87-2; 2-bromo-6-lithiopyridine, 37709-60-7; methyl 2-pyridinecarboxylate, 2459-07-6; 2-bromoethanol, 540-41-2.

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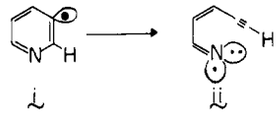

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α-Halogenation of Certain Ketones

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A variety of α-halo and α-*gem*-dihalo ketones, including the fluoro and iodo compounds, have been prepared. The scope and limitations of their syntheses have been studied. Every attempt at the preparation of 3,3-difluoro-2-butanone gave biacetyl as the only product, although the analogous *gem*-difluoropropiophenone was conveniently obtained. The synthesis of the difluorobutanone could, however, be effected with the introduction of an electronegative atom such as chlorine on the 1 position.

In the course of our stereochemical studies, the need for a number of ketones possessing a halogenated chiral carbon atom led us to investigate the halogenation, in particular fluorination, of one or both methylene hydrogens of 2-butanone, propiophenone, and 1-phenyl-2-propanone. None of the required *gem*-dihalo ketones possessing two different halogens has been previously reported.

α-Chloro or α-fluoro ketones were conveniently converted to their corresponding *gem*-bromohalo analogues by irradiation in the presence of NBS.[1] Table I lists the products with yields. Several alternate reported routes[2,3] were found to be ineffective, leading to bromoform (for methyl ketones) or polybrominated products. Bromination of monofluoroacetone with NBS gave a complex mixture.

Results and Discussion

Preparation of the Fluoro Ketones Although indirect routes have frequently been used for the preparation of fluoro methyl ketones,[4–7] direct exchange of bromine or chlorine for fluorine using metallic fluorides was used in the present work. This method, although preferred, often meets with difficulty due to the marked tendency of bromo and chloro ketones to decompose during the course of fluorination, particularly at high temperatures. The task was in finding a metal fluoride which would exchange its fluorine for halogen at a temperature low enough so as to minimize side reactions and decomposition of both the reactant and product. Mercuric fluoride was found to be a suitable metallic fluoride for the fluorination of most of the bromo ketones. These reactions are presented in Table II.

In the fluorination of **1a** with mercuric fluoride, under absolutely anhydrous conditions, a smooth exchange of bromine took place, leaving the chlorine intact and giving 3-chloro-3-fluoro-2-butanone (**1c**) together with some biacetyl. With antimony trifluoride, thallous fluoride, potassium fluoride, and potassium hydrogen difluoride, either no reaction occurred or extensive polymerization and charring resulted. Efforts to inhibit the formation of biacetyl, in the exchange reaction with mercuric fluoride, met with no success. The fluoro ketone formed an azeotropic mixture with the biacetyl and had to be purified by GLC. Pure **1c** was not hydrolyzed when boiled with water.

1c was also obtained in poor yield by the chlorination of 3-fluoro-2-butanone using *N*-chlorosuccinimide.

2-Bromo-2-chloro-1-phenyl-1-propanone (**3a**) reacted with mercuric fluoride at 85 °C to give, under optimum conditions,

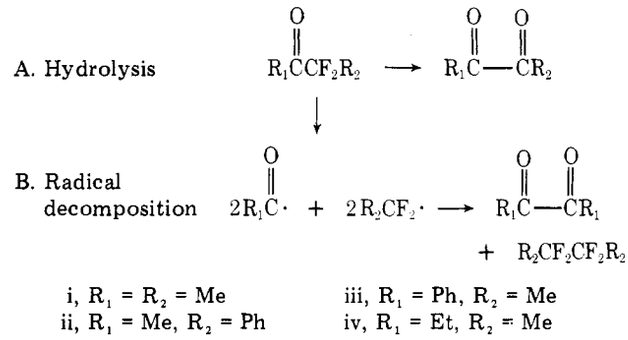
Table I. Reaction of Halo Ketones with NBS

Reactant	Registry no.	Product (yield, %)	Registry no.
1 $CH_3COCHClCH_3$	4091-39-8	**1a** $CH_3COCBrClCH_3$ (95)	63017-03-8
2 $CH_2ClCOCHFCH_3$	63017-02-7	**2a′** $CH_2ClCOCBrFCH_3$ (98)	63017-04-9
3 $C_6H_5COCHClCH_3$	6084-17-9	**3a** $C_6H_5COCBrClCH_3$ (95)	63017-05-0
4 $C_6H_5COCHFCH_3$	21120-36-5	**4a′** $C_6H_5COCBrFCH_3$ (95)	63017-06-1
5 $C_6H_5COCH_2CH_3$	93-55-0	**5b** $C_6H_5COCBr_2CH_3$ (95)	2114-03-6
6 $CH_3COCHFCH_3$	814-79-9	**6a′** $CH_3COCBrFCH_3$ (95)	63017-07-2
7 $CH_3COCH_2CH_3$	78-93-3	**7b** $CH_3COCBr_2CH_3$ (95)	2648-69-3
8 $CH_3COCHFC_6H_5$	21120-43-4	**8a′** $CH_3COCBrFC_6H_5$ (97)	57856-09-4
9 $CH_3COCH_2C_6H_5$	103-79-7	**9b** $CH_3COCBr_2C_6H_5$ (97)	63017-08-3
10 $CH_3COCHClC_6H_5$	4773-35-7	**10a** $CH_3COCBrClC_6H_5$ (97)	63017-09-4
11 $CH_3CH_2COCH_2CH_3$	96-22-0	**11b** $CH_3CH_2COCBr_2CH_3$ (15)	63017-10-7

Table II. Reaction of Bromo Ketones with Mercuric Fluoride

Reactant	Product (yield, %)
1a	**1c** $CH_3COCFClCH_3$ (32) + $CH_3COCOCH_3$
2a′	**2b′** $CH_2ClCOCF_2CH_3$ (75)
3a	**3c** $C_6H_5COCFClCH_3$ (65) + $C_6H_5COCCl{=}CH_2$ (18)
4a′ or **5b**	**4b′** $C_6H_5COCF_2CH_3$ (89)
6a′ or **7b**	$CH_3COCOCH_3$
11b	$CH_3CH_2COCOCH_2CH_3$

Scheme I



i, $R_1 = R_2 = Me$ iii, $R_1 = Ph$, $R_2 = Me$
ii, $R_1 = Me$, $R_2 = Ph$ iv, $R_1 = Et$, $R_2 = Me$

a 65% yield (by NMR) of the fluoro chloro ketone (**3c**) together with ca. 18% of 2-chloro-1-phenyl-2-propen-1-one as a result of dehydrohalogenation. A small quantity of a very volatile fraction, which was presumed to be other elimination products, was also obtained. Contrary to what was expected, no biacetyl resulted from this reaction. Similarly, the bromo fluoro ketone **4a** and the dibromo ketone **5b** gave a good yield of the *gem*-difluoro ketone **4b.** When mercuric fluoride was replaced by a mixture of mercurous fluoride and iodine (often used as a substitute for HgF_2) the reactions failed. The use of other usual metallic fluorides was also unsuccessful, as was the reaction with silver fluoride, even though this compound has been used to exchange fluorine for bromine in 1,1,1-tribromo-3,3,3-trifluoroacetone[8] and in ethyl dibromochloroacetate.[9]

Contrary to **3a,** 1-bromo-1-chloro-1-phenyl-2-propanone (**10a**) resisted all attempts toward fluorination with various metallic fluorides. Although the other ketones reacted smoothly with mercuric fluoride, this was highly reactive such that at room temperature a vigorous exothermic reaction ensued and a dark solid mass resulted. Mercuric fluoride added to **1a** at 0–5 °C appeared to give an exchange reaction, since $HgBr_2$ seemed to be formed. On warming to room temperature, however, the reaction mixture darkened and no identifiable product could be isolated. When carried out at −5 °C and using chloroform or dichloromethane as diluent, the reactions took place in the same manner. **9b** behaved similarly toward fluorination.

Partial formation of biacetyl during the synthesis of **1c** made us curious to investigate the possibility of the preparation of 3,3-difluoro-2-butanone by the same method. Thus fluorination of 3,3-dibromo-2-butanone (**7b**) and also **6a**[1] was attempted with mercuric fluoride under all the feasible conditions, which resulted in their total conversion to biactyl, giving no fluoro ketone. One could suggest that the formation of biacetyl in these reactions may be explained in terms of the immediate hydrolysis[10-11] of the possibly formed *gem*-difluoro ketone, or perhaps a free radical mechanism is taking place as shown in Scheme IB. However, the following experiments rule out the possibility of hydrolysis and suggest that the free radical mechanism is speculative: (a) The same results were obtained when reactions were performed under argon or air-free nitrogen. (b) In reactions ii and iii (Scheme I), 1-phenylpropane-1,2-dione was not obtained (Scheme IA). Neither could any fluorohydrocarbon be trapped (Scheme IB). (c) In reaction IV (Scheme I), 3,4-hexanedione was obtained, and not the hydrolytic product 2,3-pentanedione.

Since the *gem*-difluoropropiophenone could be conveniently prepared while the other two ketones could not, it was inferred that the presence of an electron-withdrawing phenyl group attached to the carbonyl may be a factor in stabilizing the formation of the *gem*-difluoro derivative. This statement is, to some extent, justified, since fluorination of 1-chloro-3-bromo-3-fluoro-2-butanone (**2a′**) with mercuric fluoride under exactly the same conditions as used for **6a′** resulted in a 90% yield (by NMR) of 1-chloro-3,3-difluoro-2-butanone **2b′**. We conclude that, although bromo ketones generally give a smooth reaction with HgF_2 with little or no decomposition, limitations are imposed on its use in some cases, due to the formation of diketones.

Fluorination with KF or KHF_2. 1-Fluoro-1-phenyl-2-propanone (**8**) was synthesized from the chloro ketone by the use of anhydrous acid potassium fluoride (KHF_2) at 230–240 ° C. It could not be prepared by the use of potassium fluoride, although this has been used for the preparation of 3-fluoro-2-butanone.[12]

Because of the difficulties encountered in the preparation of some of the *gem*-difluoro ketones using mercuric fluoride, attempts were made at their synthesis from the *gem*-dichloro precursors using KF or KHF_2. Although the α-monofluoro derivatives of such ketones could be prepared by these metallic fluorides, the dichloro ones resisted fluorination and were recovered unchanged. Similar results were obtained when using KF and crown ether[13] with acetonitrile or diethylene glycol as solvent, even though this method has been used, conveniently, to exchange bromine for fluorine in bromocyclohexanone.[13]

Preparation of the Chloro Ketones. The *gem*-dichloropropiophenone used in this investigation was prepared by the chlorination of propiophenone with sulfuryl chloride, at room temperature. A good yield of the *gem*-dichlorophenylacetone[14] and 3,3-dichlorobutanone was also obtained by a modification of Wyman's method.[15] Chlorination of 2-butanone by sulfuryl

chloride as reported by Wyman and Kaufman[15] yielded mixtures of α-chloro, α,α′-dichloro and α,α-dichloro ketone.

The ketone **2a′** could not in any way be obtained by chlorination of the *gem*-bromofluorobutanone. It was prepared by taking advantage of the unexpected behavior of 3-fluoro-2-butanone towards sulfuryl chloride to give 1-chloro-3-fluoro-2-butanone (**2**) almost quantitatively, leaving the active methylene hydrogen intact, and then brominating **2** with NBS.

Preparation of the Iodo Ketones. The iodo ketones have been studied infrequently due to their relative instability and because only few satisfactory syntheses for them are available.

For the preparation of the iodo ketones the potassium iodide interchange reaction[16] was used. This method, although generally satisfactory, is subject to pronounced steric effects. Alternative iodination with *N*-iodosuccinimide[17] gave unsatisfactory results. Iodination of the bromo ketones were generally carried out with potassium iodide in ethanol or, if hazardous, acetone as solvent. All the *gem*-haloiodo derivatives of the ketones under study were prepared. Most of the iodo ketones obtained were generally quite unstable and become viscous upon evaporation of the solvent or on standing. The order of their stability was observed to be generally iodo > bromoiodo > chloroiodo > fluoroiodo and amongst the three ketones, butanone > propiophenone > phenylacetone. When kept in carbon tetrachloride the iodobutanones were stable.

Experimental Section

NMR Spectra were recorded on a Varian T-60 instrument in CCl_4 solution with $(CH_3)_4Si$ as internal standard. Mass spectra were obtained using a Varian Mat CH5 instrument. Infrared spectra were recorded on a Pye-Unicam SP 1200 spectrometer. A Varian Aerograph gas-liquid chromatograph Model 920 equipped with thermal conductivity detectors was used for the analysis of liquids. An OV-101 on Chromosorb W60/80 mesh column was generally used. All melting and boiling points are uncorrected.

Yields are based on the mercuric fluoride whenever this metallic fluoride is used for fluorination.

Preparation of 3-Bromo-3-chloro-2-butanone (1a). **1** (10.65 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (150 mL) under illumination from a 300-W tungsten lamp. After 1 h an orange coloration appeared in the mixture and, after an additional 5 h, the color disappeared and the reaction was complete. Filtration followed by evaporation of the solvent yielded **1a** (17.63 g, 0.095 mol, 95%): bp 136 °C (667 mm); n_D^{26} 1.4850; IR 1740 cm^{-1} (C=O); NMR δ 2.20, 2.40. Anal. Calcd for C_4H_6BrClO: C, 25.91; H, 3.23; Br, 43.10. Found: C, 25.82, H, 3.01; Br, 42.93.

The semicarbazone, obtained from an aqueous solution, had mp 292–294 °C. (Anal. Calcd for $C_5H_9BrClN_3O$: C, 26.29; H, 3.94. Found: C, 26.21; H, 3.85.) Mixtures of the diastereoisomeric (−)-menthydrazone derivative was prepared by reaction with (−)-menthyl *N*-aminocarbamate, "(−)-menthydrazide[18]" in dry benzene solution. It crystallized from the same solvent, mp 142.5 °C. (Anal. Calcd for $C_{15}H_{26}BrClN_2O_2$: C, 47.22; H, 6.81. Found: C, 47.20; H, 6.79.)

By the same general method, 2-bromo-2-chloro-1-phenyl-1-propanone (**3a**) was obtained from **3**[19,20] (16.85 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 5 h. Product (23.55 g, 0.095 mol, 95%): n_D^{26} 1.5622; IR 1700 cm^{-1} (C=O); NMR δ 2.25 (s), 7.55 (m). Anal. Calcd for C_9H_8BrClO: C, 43.68; H, 3.23; Br, 32.20. Found: C, 43.50 H, 3.05; Br, 32.11.

The diastereoisomeric (−)-menthydrazone derivative, prepared and crystallized as for **1a**, had mp 121–122 °C. (Anal. Calcd for $C_{20}H_{28}BrClN_2O_2$: C, 54.15; H, 6.31. Found: C, 54.10; H, 6.45.)

1-Bromo-1-chloro-1-phenyl-2-propanone (**10a**) was obtained from **10** (16.85 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 8 h. Product (24.04 g, 0.097 mol, 97%): n_D^{26} 1.5585; IR 1735 cm^{-1} (C=O); NMR δ 2.18 (s), 7.35 (m). Anal. Calcd for C_9H_8BrClO: C, 43.68; H, 3.22; Br, 32.29. Found: C, 43.50; H, 3.39; Br, 32.35. The diastereoisomeric (−)-menthydrazone, prepared and crystallized as in **1a**, had mp 120–122 °C. (Anal. Calcd for $C_{20}H_{28}BrClN_2O_2$: C, 54.15; H, 6.31. Found C, 54.23; H, 6.50.)

3-Bromo-3-fluoro-2-butanone (**6a′**) was obtained from **6** (9.00 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 3–5 h. Product (16.2 g, 0.09 mol, 95%): bp 129–130 °C (667 mm); n_D^{26} 1.4658; IR 1740 cm^{-1} (C=O); NMR δ 2.28 (d, J_{FCH_3} = 4), 2.00 (d, J_{FCH_3} = 20). Anal. Calcd for C_4H_6BrFO; C, 28.43; H, 3.55. Found: C, 28.40; H, 3.60. The semicarbazone, obtained from an aqueous solution and crystallized from water–ethanol, had mp 220–222 °C. Anal. Calcd for $C_5H_9BrFN_3O$: C, 28.33; H, 4.24. Found: C, 28.21; H, 4.00. The diastereoisomeric (−)-menthydrazone derivative, prepared and crystallized in dry benzene, had mp 140–142 °C dec. Anal. Calcd for $C_{15}H_{26}BrFN_2O_2$: C, 49.35; H, 7.12. Found: C, 49.41; H, 7.10.

1-Bromo-1-fluoro-1-phenyl-2-propanone (**8a′**) was obtained from **8** (15.20 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 1 h. Product (22.5 g, 0.097 mol, 97%): IR (in CCl_4) 1742 cm^{-1} (C=O); NMR δ 2.44 (d, J_{FCH_3} = 4), 7.48 (m). Analytical sample was prepared by GLC at 85 °C. Anal. Calcd for C_9H_8BrFO: C, 46.79; H, 3.46. Found: C, 46.70, H, 3.21.

2-Bromo-2-fluoro-1-phenyl-1-propanone (**4a′**) was obtained from **4** (15.20 g, 0.1 mol) [prepared as in **8**, bp 35–39 °C (0.5 mm) [lit.[21] 33 °C (0.4 mm)]] and NBS (17.79 g, 0.1 mol) in 4 h. Product (22 g, 0.09 mol, 95%): IR 1698 cm^{-1} (C=O); NMR δ 2.30 (d, J_{FCH_3} = 20), 7.65 (m). Anal. Calcd for C_9H_8BrFO: C, 46.79; H, 3.46. Found: C, 46.69; H, 3.51.

1,1-Dibromo-1-phenyl-2-propanone (**9b**) was obtained from phenylacetone (13.40 g, 0.1 mol) and NBS (35.58 g, 0.2 mol) in 6–10 h. Product (28.52 g, 97%): IR 1730 cm^{-1} (C=O); NMR δ 2.36 (s), 7.46 (m). Anal. Calcd for $C_9H_8Br_2O$: C, 37.03; H, 2.74. Found: C, 37.19; H, 2.70.

2,2-Dibromo-3-pentanone (**11b**) was obtained from **11** (8.60 g, 0.1 mol) and NBS (35.58 g, 0.2 mol) in 3 h. Product (3.65 g, 0.015 mol, 15%): NMR δ 0.95 (t), 1.65 (s), 2.24 (q). Anal. Calcd for $C_5H_8Br_2O$: C, 24.62; H, 3.28; Br, 65.53. Found: C, 24.51; H, 3.02; Br, 65.41. Other products: 2,4-dibromo-3-pentanone (48%) and 2,2,4-tribromo-3-pentanone (20%).

Preparation of 1-Fluoro-1-phenyl-2-propanone (8). **10** (33.70 g, 0.19 mol) was added dropwise to a vigorously stirred mixture of finely ground and thoroughly dried potassium hydrogen fluoride (78.08 g, 1 mol) and diethylene glycol (120 g) at 230–240 °C. The fluorinated material was allowed to distill through a downward condenser by applying a slight vacuum. The temperature at the still head was maintained at 80–110 °C by controlling the rate of addition of the chloro ketone. The contents of the reaction flask were then extracted thoroughly with CCl_4 and the extract was added to the distillate. Fractionation through an efficient column gave **8** (12.50 g, 0.082 mol, 43%): IR 1725 cm^{-1} (C=O); NMR δ 2.18 (d, J_{FCH_3} = 4), 5.55 (d, J_{HF} = 50), 7.25 (m). The spectral data agreed well with those reported by Newman and Angier,[22] who obtained the compound as a side product in the preparation of α-nitro epoxides.

Preparation of 3-Chloro-3-fluoro-2-butanone (1c). (i) A carefully dried apparatus initially protected with $CaCl_2$ tube was used. Finely ground mercuric fluoride (15 g, 0.06 mol) was added all at once to carefully purified **1a** (25 g, 0.13 mol) in a 50-mL round-bottom flask equipped with a condenser and receiver immersed in dry ice–methanol. The vigorously stirred mixture was quickly raised to, and maintained at, 140 °C; the visible reaction ensued after a few minutes. The temperature was kept between 140 and 160 °C until the reaction was complete as shown by a color change of mercuric fluoride from red-orange to dark brown. The contents of the flask were then distilled by applying a slight vacuum and the products distilling over between 70 and 100 °C were collected. Fractionation of the liquid so obtained gave 5.55 g of a mixture, bp 92–96 °C, containing **1c** and biacetyl in the ratio of 54:45 (by NMR). Isolation of pure **1c** from this mixture was effected by GLC Autoprep. at 50 °C. It had: bp 102–103 °C; IR 1745 cm^{-1} (C=O); NMR δ 1.62 (d, J_{FCH_3} = 20), 2.02 (d, J_{FCH_3} = 4); mass spectrum *m/e* 126, 124 (M^+). Anal. Calcd for C_6H_6ClFO: C, 38.59; H, 4.82. Found: C, 38.40; H, 4.93. The diasteoisomeric (−)-menthydrazone derivative, prepared and crystallized in CCl_4 solution, had mp 200 °C. (Anal. Calcd for $C_{15}H_{26}ClFN_2O_2$: C, 56.19; H, 8.11. Found: C, 56.18; H, 8.01.)

(ii) **6** (9.00 g, 0.1 mol), NCS (13.35 g, 0.1 mol), and 3 mg of benzoyl peroxide were reacted in benzene (under UV irradiation) and worked up as in the preparation of **1a** to give **1c** (0.32 g, 0.025 mol, 2.5%).

Preparation of 2-Chloro-2-fluoro-1-phenyl-1-propanone (3c). **3a** (24.75 g, 0.1 mol) and HgF_2 (7.5 g, 0.03 mol) were reacted as in the preparation of **1c**. Reaction ensued at 85 °C and was raised up to 125 °C until the reaction was complete. Repeated fractionation of the product gave nearly pure **3c** (3.64 g, 0.019 mol, 65%). Final purification was effected with GLC at 70 °C: IR 1705 (C=O); NMR δ 2.00 (d, J_{FCH_3} = 20), 7.60 (m); mass spectrum *m/e* 188,186 (M^+). Anal. Calcd for C_9H_8ClFO: C, 67.95, H, 4.28. Found: C, 57.79, H, 4.12.

Also obtained was 2-chloro-1-phenyl-2-propen-1-one (0.90 g, 18%): IR 1580 (C=C), 1690 cm^{-1} (C=O); NMR showing the characteristic

AB system with δ 5.98, 5.83 (d, J_{AB} = 2 Hz), 7.60 (m, Ph). Anal. Calcd for C_9H_7ClO: C, 64.90; H, 4.20. Found: C, 65.20, H, 4.38.

A volatile fraction (1 g) boiling at 55–60 °C, which remained unidentified, was also obtained.

Reaction of 1-Bromo-1-chloro-1-phenyl-2-propanone (10a) with Mercuric Fluoride. A. Mercuric fluoride (7.5 g, 0.03 mol) was added all at once at 0–5 °C to **10a** (24.75 g, 0.1 mol). A vigorous reaction started immediately and the contents of the reaction flask became solid. No identifiable product could be isolated; the NMR of the product on warming to room temperature consisted of numerous peaks.

B. Mercuric fluoride was gradually added to **10a** dissolved in pure dry $CHCl_3$ through a section of 1.25-in. rubber tubing which was closed just above the neck by a screw clamp. The contents of the reaction flask were maintained between 5 and 10 °C under vigorous stirring until the addition of HgF_2 was complete. The reaction mixture was then filtered and the residue washed with chloroform, worked up, and dried over calcium chloride. Upon removal of chloroform the residue was found to contain ca. 50% of the unchanged starting material together with other unidentified mixtures. Repetition of this experiment in the presence of dry pyridine in order to prevent possible polymerization and side reactions gave similar results to above.

Reaction of 3,3-Dibromo-2-butanone (7b)[23] with Mercuric Fluoride. Mercuric fluoride (15.00 g, 0.06 mol) was added to **7b** (22.98 g, 0.1 mol) and the temperature was quickly raised to 80 °C where reaction ensued. The temperature was kept at 115–120 °C until the visible reaction subsided. The contents of the flask were allowed to distill over. The first fraction, bp 70–75 °C (4.90 g, 95%), was found to be biacetyl (by NMR, GLC, and preparation of its semicarbazone derivative); the second fraction, bp 90–130 °C, was unchanged **7b** (ca. 2.5 g). Various modifications of this reaction under argon or air-free nitrogen gave only biacetyl. Similarly, the reaction 2,2-dibromo-3-pentanone with HgF_2 gave 3,4-hexanedione as the only product (90%).

Preparation of 2,2-Difluoro-1-phenyl-1-propanone (4b'). A. Mercuric fluoride (30.0 g, 0.12 mol) was added to **5b**[24] (58.37 g, 0.2 mol) at 50 °C. The reaction mixture was then stirred vigorously and the temperature raised to 120–125 °C, where the reaction started. Upon subsidence of the visible reaction (2–3 min), stirring was discontinued and 10 mL of pure CCl_4 was quickly added to the reaction mixture. This mixture was then filtered and the filtrate was fractionated to give **4a** (1.4 g, 5%) and **4b'** (18.4 g. 0.107 mol, 90%): IR 1705 cm^{-1} (C=O) (lit. 5.85[25] prepared from the corresponding alkyne and OF_2); NMR δ 1.76 (t, J_{FCH_3} = 19), 7.68 (m).

B. Mercuric fluoride (15.0 g) and **4a** (23.0 g) reacted and worked up as above gave **4b** (9.5 g, 95%) and unchanged **4a** (5.2 g).

Reaction of 9b with Mercuric Fluoride. 9b (15 g) was dissolved in 20 mL of $CHCl_3$ and mercuric fluoride (6 g) was added to it gradually at 5 °C. The reaction flask, which becomes warm, was kept between 2 and 7 °C until the addition of HgF_2 was complete. Analysis of the reaction mixture by NMR did not show the presence of 1,1-difluoro-1-phenyl-2-propanone,[26] although some characteristic triplet peaks indicative of fluorine coupling were present in the NMR spectrum of the mixture.

Preparation of 1-Chloro-3-fluoro-2-butanone (2). 6 (9.0 g, 0.1 mol) was placed in a 50-mL round-bottom flask and sulfuryl chloride (13.49 g, 0.1 mol) was added to it dropwise at room temperature during 2–3 h while stirring vigorously. The reaction mixture was kept stirring overnight at room temperature. Fractionation of the dark mixture gave unchanged **6** (0.5 g) and almost pure **2** (11.19 g, 90%). Analytical sample was obtained by GLC at 65 °C: n_D^{26} 1.4280; IR 1753 cm^{-1} (C=O); NMR δ 1.52 (dd, J_{FCH_3} = 22, J_{HCH_3} = 6), 5.08 (d, J_{HF} = 50). 4.40 (d, J_{FCH_2} = 4). Anal. Calcd for C_4H_6ClFO: C, 38.59; H, 4.82. Found: C, 38.82; H, 4.91.

Preparation of 3-Chloro-1-fluoro-1-phenyl-2-propanone. 8 (15.20 g, 0.1 mol) reacted with sulfuryl chloride (13.49 g, 0.1 mol) as above at 25 °C during 5 h to give the title compound (15.2 g, 85%) based on NMR. Analytical sample was obtained by GLC at 65 °C: IR 1746 cm^{-1} (C=O); NMR δ 4.10 (d, J_{FCH_2} = 4), 5.60 (d, J_{HF} = 49), 7.10 (m). Anal. Calcd for C_9H_8FClO: C. 57.95; H, 4.28. Found: C, 57.75; H, 4.52.

Preparation of 1-Chloro-3-bromo-3-fluoro-2-butanone (2a'). 2 (12.44 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (150 mL) as in **1a** for 6 h and worked up to give **2a** (20 g, 98%): IR 1760 cm^{-1} (C=O); NMR δ 2.20 (d, J_{FCH_3} = 22), 7.70 (d, J_{FCH_2} = 3). Anal. Calcd for $C_4H_5BRClFO$: C, 23.62; H, 2.45. Found: C, 23.42; H, 2.51.

3-Chloro-1-bromo-1-fluoro-1-phenyl-2-propanone. 3-Chloro-1-fluoro-1-phenyl-2-propanone (18.65 g) and NBS taken in molar ratios reacted as above for 5–8 h to give the title compound in 96% yield: IR 1755 cm^{-1} (C=O); NMR δ 4.30 (d, J_{FCH_2} = 4), 7.22 (m). Anal. Calcd for $C_9H_7BrClFO$: C, 40.72; H, 2.63. Found: C, 40.41; H, 2.80.

Preparation of 1,3-Difluoro-2-butanone. 2 (12.44 g, 0.1 mol) was reacted with potassium fluoride (8.7 g) in diethylene glycol (10 mL) at 180–200 °C in the usual manner. When product was distilled under reduced pressure while **2** was being added, the liquid mixture so obtained was found to contain ca. 3 g of the title compound by NMR. Analytical sample was obtained by GLC at 45 °C: IR 1755 cm^{-1} (C=O); NMR 1.50 (dd, J_{HCH_3} = 6, J_{FCH_3} = 22), 3.95 (dd, J_{FCH_2} = 4,44), 5.00 (ddq, J_{HF} = 50). Anal. Calcd for $C_4H_6F_2O$: C, 44.47; H, 5.55. Found: C, 44.31; H, 5.20. The major portion of the mixture consisted of a compound which could possibly be an olefin (its NMR having a doublet of doublets at δ 4.6 and 5.4 (J = 46 and 4 Hz). When, however, the product is left in the ethylene glycol/KF mixture and is distilled at the end of the reaction, the sole product is the presumed olefin, as is the case where KHF_2 is used for this fluorination.

Preparation of 1-Chloro-3,3-difluoro-2-butanone (2b'). 2a (18 g, 0.08 mol) and mercuric fluoride (5.7 g, 0.024 mol) were reacted as in **1c**. Threshhold temperature for this fluorination was at 145–150 °C. The product distilling over from the downward condenser was collected in the range 70–80 °C and was subjected to repeated fractionation to give **2b'** (2.68 g, 75%): IR 1765 cm^{-1} (C=O); NMR δ 1.68 (t, J_{FCH_3} = 19), 4.40 (t, J_{FCH_2} = 1). Anal. Calcd for $C_4H_5ClF_2O$: C, 33.72; H, 3.50 Found: C, 33.62; H, 3.71.

Preparation of 2,2-Dichloro-1-phenyl-1-propanone. To propiophenone (13.41 g), sulfuryl chloride (27 g) was added during 20 h at room temperature while stirring vigorously. Analysis of the mixture by NMR indicated the presence of 50% title compound together with ca. 40% of the monochloro ketone. This is a much more convenient method of preparation than that reported in the literature.[27] The *gem*-dichloro analogues of phenylacetone and 2-butanone were prepared similar in 80% yield, respectively (reaction times 25–30 h).

Preparation of 3-Iodo-2-butanone. A mixture of 3-bromo-2-butanone (13.28 g, 0.08 mol) and KI (16.60 g, 0.1 mol) in 20 mL of absolute alcohol was refluxed for 2 h. The reaction mixture was then cooled, dried with magnesium sulfate, and extracted with ether. Fractionation of the evaporated extract gave the title compound (15.12 g, 95%): bp 148–150 °C dec (667 mm); n_D^{26} 1.4288; IR 1730 cm^{-1} (C=O); NMR δ 2.40 (s), 1.80 (d, J_{HCH_3} = 6). 4.80 (q, J_{HCH_3} = 6). Anal. Calcd for C_4H_7IO: C, 24.27; H, 3.52. Found: C, 24.58; H, 3.15. The pure sample should be kept in a dark bottle in vacuo. Under ordinary conditions it partially decomposes within a few hours and a waxy polymeric product results within a week. The diastereoisomeric (−)-menthydrazone derivative was prepared in dry benzene solution, mp 188–190 °C dec. This derivative partially decomposes and turns brown when kept for a few days. The semicarbazone (from an aqueous solution) had mp 212–214 °C dec.

Preparation of 3-Bromo-3-iodo-2-butanone. 3-Iodo-2-butanone (19.79 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (170 mL) as in **1a**. The reaction was stopped after 5 h to give 10% (by NMR) of the title compound. It is worthy of mention that 3-bromobutanone under the same conditions gave 95% of the dibromobutanone after 5 h. When the reaction was continued for 30–35 h nearly 95% of the title compound was obtained in pure form. This ketone, although more resistant toward decomposition than the chloroiodobutane while evaporating the solvent, could not be isolated from the solvent. It had: IR (CCl_4) 1730 cm^{-1}; NMR δ 2.42 (s), 2.61 (s). Its (−)-menthydrazone prepared in CCl_4 solution had mp 228–230 °C dec. Anal. Calcd for $C_{15}H_{26}BrIN_2O_2$: C, 42.09; H, 6.07. Found: C, 41.63; H, 5.70.

Preparation of 3-Chloro-3-iodo-2-butanone. A mixture of **1a** (13.28 g, 0.08 mol) and KI (16.6 g, 0.1 mol) were refluxed in 20 mL of absolute alcohol for 2 h to give a liquid mixture containing 9.3 g (50%) of the title compound. Separation of the mixture by column chromatography using silica gel and CCl_4 gave the iodo ketone in pure form (fifth fraction): IR 1738 cm^{-1} (C=O); NMR δ 2.32 (s), 2.60 (s). The iodo ketone was pure by NMR, but evaporation of its solvent (CCl_4) even under reduced pressure, in order to obtain an analytical sample, resulted in its partial decomposition. Its menthydrazone derivative prepared in CCl_4 solution had mp 208–210 °C dec. Anal. Calcd for $C_{15}H_{26}ClIN_2O_2$: C, 42.24; H, 6.09. Found: C, 42.41; H, 6.30. The semicarbazone derivative prepared in a split-phase CCl_4–H_2O medium had mp 288 °C dec. Other fractions obtained had only a singlet in their NMR and were not investigated further.

Preparation of 3-Fluoro-3-iodo-2-butanone. A mixture of **6a** (13.52 g, 0.08 mol) and KI (16.6 g, 0.1 mol) in dry acetone (25 mL) was stirred at room temperature for 3 h. Half of the acetone was then evaporated under reduced pressure. The dark red mixture obtained was found to contain the title compound (60% by NMR): IR was obtained by evaporating nearly all the acetone under reduced pressure

and immediately adding CCl_4 to the residue, IR 1735 cm^{-1} (C=O); NMR δ 2.38 (d, J_{FCH_3} = 4), 2.18 (d, J_{FCH_3} = 20). The compound decomposes after 2 days even when kept in CCl_4. The diastereoisomeric (−)-menthydrazone prepared in CCl_4 solution had mp 162–164 °C dec. Anal. Calcd for $C_{15}H_{26}FIN_2O_2$: C, 49.08; H, 7.07. Found: C, 50.69; H, 6.50. Attempted preparation of the title compound in ethanol as solvent gave decomposed mixtures. No reaction occured without the use of any solvent.

Other iodo compounds which were prepared by the same general method but could not be isolated in pure form due to their instability were: 1-Iodo-1-phenyl-2-propanone (98%): IR 1715 cm^{-1} (C=O); NMR δ 2.35 (s), 7.32 (m). 2-Iodo-1-phenyl-1-propanone (26.5%): IR 1693 cm^{-1} (C=O); NMR δ 2.10 (d, J_{HCH_3} = 6), 6.10 (q, J_{HCH_3} = 6), 7.65 (m). 1-Chloro-1-iodo-1-phenyl-2-propanone (96%): IR 1733 cm^{-1} (C=O); NMR δ 2.35 (s), 7.38 (m). 2-Chloro-2-iodo-1-phenyl-1-propanone (13%): IR 1695 cm^{-1} (C=O); NMR δ 2.40 (s), 7.75 (m). 1-Fluoro-1-iodo-1-phenyl-2-propanone (95%): IR 1723 cm^{-1} (C=O); NMR δ 2.30 (d, J_{FCH_3} = 4), 7.40 (m). 2-Fluoro-2-iodo-1-phenyl-1-propanone (35%): IR 1696 cm^{-1} (C=O); NMR δ 2.54 (d, J_{FCH_3} = 20), 7.78 (m). 1-Bromo-1-iodo-1-phenyl-2-propanone (98%) [IR 1720 cm^{-1} (C=O); NMR δ 2.30 (s), 7.60 (m)] and 2-bromo-2-iodo-1-phenyl-1-propanone (68%) [IR 1690 cm^{-1} (C=O); NMR δ 2.35 (s), 7.60 (m)] were also prepared by bromination of the corresponding iodo-compounds with NBS in the general manner.

Registry No.—**1a** semicarbazone, 63017-11-8; **1a** (−)-menthydrazone epimer I, 63017-12-9; **1a** (−)-menthydrazone epimer II, 63017-13-0; **1c**, 63017-14-1; **1c** (−)-menthydrazone epimer I, 63017-15-2; **2c** (−)-menthydrazone epimer II, 63017-16-3; **2b′**, 63017-17-4; **3a** (−)-menthydrazone epimer I, 63017-18-5; **3a** (−)-menthydrazone epimer II, 63017-19-6; **3c**, 63017-20-9; 1,3-difluoro-2-butanone, 63058-87-7; **4b′**, 703-17-3; **6a′** semicarbazone, 63017-21-0; **6a′** (−)menthydrazone epimer I, 63017-22-1; **6a** (−)-menthydrazone epimer II, 63017-23-2; **10a** (−)-menthydrazone epimer I, 63017-24-3; **10a** (−)-menthydrazone epimer II, 63017-25-4; 2 chloro-1-phenyl-2-propen-1-one, 19233-44-4; 3-chloro-1-fluoro-1-phenyl-2-propanone, 63017-26-5; 3-chloro-1-bromo-1-fluoro-1-phenyl-2-propanone, 63017-27-6; 2,2-dichloro-1-phenyl-1-propanone, 57169-51-4; 3-iodo-2-butanone, 30719-18-7; 3-bromo-2-butanone, 814-75-5; 3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-28-7; 3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-29-8; 3-iodo-2-butanone semicarbazone, 63017-30-1; 3-brono-3-iodo-2-butanone, 63017-31-2; 3-bromo-3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-32-3; 3-bromo-3-iodo-2-butanone (−)-menthydrazone epimer II, 63067-33-4; 3-chloro-3-iodo-2-butanone, 63017-34-5; 3-chloro-3-iodo-2-butanone (−)-menthydrazone epimer I, 63058-88-8; 3-chloro-3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-35-6; 3-chloro-3-iodo-2-butanone semicarbazone, 63107-36-7; 3-fluoro-3-iodo-2-butanone, 63017-37-8; 3-fluoro-3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-38-9; 3-fluoro-3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-39-0; 1-iodo-1-phenyl-2-propanone, 63017-40-3; 2-iodo-1-phenyl-1-propanone, 6084-15-7; 1-chloro-1-iodo-1-phenyl-2-propanone, 63017-41-4; 2-chloro-2-iodo-1-phenyl-1-propanone, 63017-42-5; 1-fluoro-1-iodo-1-phenyl-2-propanone, 63017-43-6; 2-fluoro-2-iodo-1-phenyl-1-propanone, 63017-44-7; 1-bromo-1-iodo-1-phenyl-2-propanone, 63017-45-8; 2-bromo-2-iodo-1-phenyl-1-propanone, 63017-46-9.

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Steric Effects. 9. Substituents at Oxygen in Carbonyl Compounds

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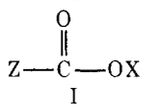
Twenty-nine sets of basic hydrolyses rate constants for alkyl acetates, formates, propionates, and benzoates; four sets of acid-catalyzed hydrolysis rate constants of alkyl acetates; one set of rate constants for the vapor-phase esterification of acetic acid with alcohols; and one set of rate constants for the reaction of 4-nitrobenzoyl chloride with alcohols were correlated by the modified Taft equation using ν_X, ν_{CH_2X}, and ν_{OX} constants. Best results were obtained with the ν_{OX} constants which were defined in this work. Forty values of ν_{OX} are given. The successful correlation with ν_{CH_2X} verified the validity of the equation $\nu_{Z_1X} = \nu_{Z_2X} + c$. The magnitude of ψ as a function of the structure of the substrate is described.

In many data sets of reaction rates of carbonyl compounds, the effect of substitution at an oxygen atom has been studied. In particular, rates of ester hydrolysis of I, where Z is a constant substituent and X is permitted to vary, have been examined. The first attempt at handling steric effects of the X group is due to Taft,[1] who proposed E_S values for these



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groups and pointed out[2] that E_{SX} and E_{SZ} may differ significantly from each other when X = Z. In this work, effects of R in the set RCH_2OAc were correlated with the Taft equation

$$\log (k/k^0) = \delta E_S \quad (1)$$

using E_{SZ} values. Results were good for a set of eight substituents, although two of the substituents had to be excluded from the set. It seemed to us of interest to extend our previous investigation[3–10] to this topic. For this purpose, we examined