solved in toluene (500 ml.) and precipitated by the addition of 5 ml. of ethanolamine; weight of the ethanolamine ester of the borinate, 6.95 g. (17% yield), m.p. 235–240°. Recrystallization of 5.14 g. of this ester yielded 4.38 g. of purified material, m.p. 236–237°.

Anal.[6] Calcd. for $C_{14}H_{14}ONBr_2B$: B, 2.826; equiv. wt., 383. Found: B, 2.90; equiv. wt. (by titration with hydrochloric acid), 382.

The solution from the acid titration (acetone–water solution) was extracted with ether. The organic material thus obtained melted at 82–84° after recrystallization from petroleum heptane. The melting point previously reported for bis-*p*-(bromophenyl)borinic acid was 113°.[2c]

Diethanolamine Esters of Arylboronic Acids.—These esters were formed readily by the reaction of diethanolamine with an arylboronic acid. They are high melting solids and can serve as derivatives of the boronic acids.

A mixture of 12.20 g. of benzeneboronic acid, 10.84 g. of diethanolamine and 800 ml. of toluene was distilled until the volume of the solution was about 400 ml. After cooling, the precipitate was collected and washed with dry ether; weight 18.96 g., m.p. 212–214°. A portion (7.12 g.) was dissolved in 50 ml. of hot ethanol and reprecipitated by addition of ligroin; weight 6.10 g. (85%), m.p. 214–215°. The molecular weight of this material determined by the Rast method was over 600.

The derivatives of *p*-bromobenzeneboronic acid and *p*-methoxybenzeneboronic acid were prepared similarly. In the case of naphthaleneboronic acid, the diethanolamine derivative was sufficiently insoluble that it could be precipitated directly from an alcohol–water solution. Thus, the addition of 3 ml. of diethanolamine in 3 ml. of water to a solution of 4 g. of naphthaleneboronic acid in 10 ml. of alcohol and 5 ml. of water yielded 4.94 g. (88%) of the derivative.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY OF THE HEBREW UNIVERSITY, HADASSAH MEDICAL SCHOOL]

ω-Fluoroacetophenone. II.[1] Substitutions in the Fluoromethyl Group of ω-Fluoroacetophenone

BY FELIX BERGMANN, ABRAHAM KALMUS AND SANDER VROMEN[2]

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Only one hydrogen atom of the fluoromethyl group of ω-fluoroacetophenone can be substituted by halogens. Nucleophilic reagents replace only the second halogen in the disubstituted acetophenones, but leave the fluorine atom untouched. The new halogen derivatives are all powerful lachrymators.

Since fluorine possesses the highest electronegativity among all elements but does not exert any appreciable steric interference with other substituents, it appeared of interest to study substitution reactions of the fluoromethyl group of ω-fluoroacetophenone (I). This ketone does not react with elementary chlorine under conditions which permit an almost quantitative chlorination of acetophenone itself. Likewise, N-chlorosuccinimide was without effect, but in the presence of benzoyl peroxide in boiling carbon tetrachloride a trace of lachrymatory material was formed. Gryszkiewicz-Trochimowski[3] achieved chlorination of fluoroacetyl chloride by sulfuryl chloride in a closed vessel at 150–160° and obtained about 50% yield of the monochloro derivative. We have observed that a solution of I in sulfuryl chloride undergoes a spontaneous reaction at room temperature. Gas evolution sets in after an induction period of about 30 min and stops after 15–16 hours. From this mixture α-chloro-α-fluoroacetophenone (IIa) can be isolated in 75% yield. Peroxide has no influence on the speed or yield of this reaction. The chlorination of I thus can be considered as an electrophilic substitution, but the curious role of sulfuryl chloride is not understood.

In view of these results it is surprising that bromination of I can be accomplished with elementary bromine in ether in presence of a catalytic amount of aluminum chloride. The yield of α-bromo-α-fluoroacetophenone (IIb) was almost quantitative. On the other hand, no reaction is observed with iodine or its monochloride. The iodo derivative (IIc) was prepared by halogen exchange between IIa or b and potassium iodide in ethanol, in analogy to the method applied by Swarts[4] to the synthesis of ethyl iodofluoroacetate. In this series only the halogen beyond fluorine can be removed by direct electrophilic substitution, whereas, *e.g.*, in α,α-dibromoacetophenone both halogens are exchangeable.[5]

The direct replaceability of *one* halogen only in the ketones IIa–c was demonstrated in other examples also. Thus, with ammonium thiocyanate, α-fluoro-α-thiocyanoacetophenone (IId) was formed and with trimethylamine the quaternary ammonium salt III. However, with other nucleophilic reagents, complicated secondary reactions took place, which will be reported in a future publication.

The facile introduction of *one* additional halogen atom into the fluoromethyl group of I contrasts sharply with the resistance of compounds IIa-c toward further halogenation. They were not attacked by boiling sulfuryl chloride or by bromine under a variety of experimental conditions, although α,α-dichloro- or dibromoacetophenone can be halogenated further.[6] This might give the impression that only one hydrogen atom of the $-CH_2F-$ group could be substituted. However, condensation with benzaldehyde produces α-fluorobenzalacetophenone (IV) in 40% yield.

The fluorine atom in the ketones IIa-d is, however, not entirely inert. Thus they all give the same dioxime of m.p. 172°[7] and the same bis-semicarba-

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[1] Part I. F. Bergmann and A. Kalmus, THIS JOURNAL, **76**, 4137 (1954).

[2] Part of a Ph.D. thesis, submitted to the Hebrew University, 1955.

[3] E. Gryszkiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

[4] F. Swarts, *Memoires couron.*, *Acad. roy. Belg.*, 61 (1901); *Chem. Zentr.*, **74**, I, 11 (1903).

[5] A. Collet, *Bull. soc. chim.*, [3] **23**, 830 (1900).

[6] J. G. Aston, J. D. Newkirk, J. Dorsky and D. M. Jenkins, THIS JOURNAL, **64**, 1413 (1942).

[7] A. Russanow, *Ber.*, **24**, 3500 (1891).

zone of m.p. 237°[8] as phenylglyoxal or α,α-dichloroacetophenone. Similarly they are degraded by sodium acetate in ethanol to mandelic or benzoic acid. In all these reactions general base catalysis is involved.

The esters of chloro- and bromofluoroacetic acid possess a pleasant smell.[3,9] The halogenated fluoroacetophenones on the other hand are powerful lachrymators, comparable in strength to the non-fluorinated homologs. Since pure α,α-dichloro- or dibromoacetophenones are not tear gases, the interesting fact emerges that only in the acetophenone series identical biological effects are produced by the combination $-COCH_2Hal$ and $-COCHFHal$, where Hal = Cl, Br or I.

Comparison of the physical properties of the halogen derivatives of acetophenone and ω-fluoroacetophenone reveals the following features: (a) If one hydrogen is replaced by Cl, Br or I in acetophenone the m.p.'s. follow the series 20, 59, 50, 30° with ω-chloroacetophenone being the member of the series with the highest melting point. In ω-fluoroacetophenones, however, the corresponding values are 29, 44.5, 54.5, 68, showing a progressive rise with increasing size of the substituent. (b) The ultraviolet absorption maximum in fluoroacetophenone itself shifts from its position in acetophenone by about 40 Å. toward longer wave lengths, while in the halogenated derivatives the shift is greater (70–80 Å.).

$$\underset{\text{I}}{C_6H_5COCH_2F} \longrightarrow \underset{\text{II}}{C_6H_5COCHF{-}R}$$

a, R = Cl; b, R = Br
c, R = I; d, R = SCN

$$\underset{\text{III}}{C_6H_5COCHFN(CH_3)_3{}^+\,Br^-} \qquad \underset{\text{IV}}{C_6H_5COCF{=}CHC_6H_5}$$

Experimental[10]

α-Chloro-α-fluoroacetophenone (IIa),—ω-Fluoroacetophenone (10 g.) was dissolved in sulfuryl chloride (15 g. = 1.5 equiv.). After 30 minutes standing at room temperature, evolution of HCl set in and continued for 15–16 hours. When the mixture was poured on ice, a white precipitate, producing intense lachrymation and unbearable headache was obtained. The material was dissolved in ether, washed with bicarbonate and dried. The ether was evaporated and the residue recrystallized from petroleum ether yielding large plates of m.p. 44.5°, yield 9.3 g.; λ_{max} 2530, log ϵ_{max} 4.05.

Anal. Calcd. for C_8H_6ClFO: C, 55.7; H, 3.5. Found: C, 55.9; H, 3.5.

With semicarbazide acetate in dilute ethanol a bis-semicarbazone of m.p. 236–237° was obtained, which crystallized from butyl acetate–pyridine in rods.

Anal. Calcd. for $C_{10}H_{12}O_2N_6$: C, 48.5; H, 4.9. Found: C, 48.6; H, 4.9.

The bis-oxime, after crystallization from dilute ethanol, formed colorless prisms of m.p. 172–173°.

Anal. Calcd. for $C_8H_8O_2N_2$: C, 58.5; H, 4.9. Found: C, 58.7; H, 5.2.

The bis-2,4-dinitrophenylhydrazone crystallized from pyridine in red needles of m.p. 280° dec.

Anal. Calcd. for $C_{20}H_{14}N_8O_8$: C, 48.6; H, 2.8. Found: C, 49.0; H, 3.0.

α-Bromo-α-fluoroacetophenone (IIb).—ω-Fluoroacetophenone (13.8 g.) and aluminum chloride (0.2 g.) were dissolved in dry ether (20 ml.). The mixture was cooled to 0° and bromine (16 g.) added dropwise. The excess bromine was removed by a current of air, then benzene added and the solution washed with bicarbonate and dried. The solid residue, which remained after removal of the solvent, was recrystallized twice from ligroin, with addition of charcoal; white plates of m.p. 54–54.5°, with most powerful lachrymating effect, yield 20 g.; λ_{max} 2580, log ϵ_{max} 4.02.

Anal. Calcd. for C_8H_6BrFO: C, 44.2; H, 2.8. Found: C, 44.4; H, 3.0.

This ketone gave a bis-semicarbazone and bis-oxime, identical with the derivatives described above.

α-Iodo-α-fluoroacetophenone (IIc).—To a solution of ketone IIb (4.3 g.) in ethanol (20 ml.) was added a solution of potassium iodide (3.3 g.) in water (3 ml.) and ethanol (30 ml.). Precipitation of potassium bromide started immediately and the solution slowly turned dark. After 12 hours standing at room temperature, the solution was filtered and the alcohol distilled off. The residue, which produced painful lachrymation and throbbing headache, was dissolved in ether, washed with thiosulfate and dried. After several crystallizations from petroleum ether white needles of m.p. 67–68° can be obtained, which turn brown slowly, especially upon exposure to light; yield 5.1 g.; λ_{max} 2550, log ϵ_{max} 3.95. Only in the dark can this material be preserved for 1–2 weeks without marked decomposition. The compound was recrystallized and analyzed immediately.

Anal. Calcd. for C_8H_6FIO: C, 36.4; H, 2.3. Found: C, 36.7; H, 2.35.

From this compound the same ketonic derivatives were obtained as described before.

α-Fluoro-α-thiocyanoacetophenone (IId).—To a solution of sodium or ammonium thiocyanate (2.5 g.) in ethanol (20 ml.) was added slowly a solution of IIb (5 g.) in ethanol (10 ml.). The mixture became warm and, after a few minutes, precipitation of inorganic bromide set in. After 12 hours standing at room temperature, the solvent was removed and the residue extracted several times with boiling ligroin. Since the product tends to smear, it is necessary to induce crystallization by scratching; glistening rods of m.p. 62°, yield 4 g.

Anal. Calcd. for C_9H_6FNOS: C, 55.4; H, 3.1; N, 7.2. Found: C, 55.3; H, 3.5; N, 6.9.

This ketone gave the same bis-dinitrophenylhydrazone as described before.

α-Fluoroacetophenone-α-trimethylammonium Bromide (III).—α-Bromo-α-fluoroacetophenone (5 g.) was suspended in 40% aqueous trimethylamine (10 ml.). After evaporation of the liquid layer, another 10 ml. of the amine was added. The residue was triturated with ethyl acetate and the solid portion filtered off; yield 3.5 g., 55%. After crystallization from isopropyl alcohol white plates of m.p. 159–160° were obtained.

Anal. Calcd. for $C_{11}H_{15}BrFNO$: C, 47.8; H, 5.4; N, 5.1. Found: C, 48.2; H, 5.75; N, 5.1.

The salt was dissolved in 60% perchloric acid, whereupon hydrogen bromide was evolved. After 10 min. water was added to precipitate the perchlorate of III. It crystallized from water in glistening plates of m.p. 190–191°.

Anal. Calcd. for $C_{11}H_{15}ClFNO_5$: ClO_4, 33.7. Found: ClO_4, 33.3.

α-Fluorobenzalacetophenone (IV).—To 10% sodium hydroxide (46 ml.) was added a solution of ω-fluoroacetophenone (10 g.) in ethanol (20 ml.), so that a yellow emulsion was formed. Benzaldehyde (10 g.) was added under vigorous stirring, while the temperature was kept below 23°. After 4 hours stirring the mixture was left in a refrigerator. The next day, the yellow oil was separated and steam distilled to remove the excess aldehyde. The residue, upon trituration with methanol, gave a white solid. This formed bundles of needles of m.p. 184–185°, when recrystallized from butyl acetate, yield 1.6 g.

Anal. Calcd. for $C_{16}H_{13}FO_2$: C, 75.0; H, 5.1; mol. wt., 256. Found: C, 75.0; H, 5.0; mol. wt., 263; 271 (cryoscopically in benzene).

The analysis indicates that this product is formed from

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[8] A. Koetz, *J. prakt. Chem.*, [2] **90**, 304 (1914).

[9] F. Swarts, *Bull. Acad. Roy. Belg.*, **36**, 532 (1898); *Chem. Zentr.*, **70**, I, 588 (1899).

[10] All melting points are uncorrected. All absorption spectra were measured in 95% ethanol with a Beckman ultraviolet spectrophotometer. Carbon and hydrogen determinations were carried out by Mrs. Goldstein according to the method of W. Bodenheimer and M. Goldstein, *Bull. Res. Council, Israel*, III, 53 (1953).

two molecules of I by elimination of HF. Its structure was not elucidated.

The mother liquor of the above product was fractionated *in vacuo*. A light yellow oil distilled at 130° (0.4 mm.), which solidified spontaneously. From methanol, white plates of m.p. 59–60° were obtained; yield 7 g. The ultraviolet spectrum of this compound (IV) was practically identical with that of benzalacetophenone.

Anal. Calcd. for $C_{15}H_{11}FO$: C, 79.6; H, 4.9. Found: C, 79.6; H, 5.1.

The 2,4-dinitrophenylhydrazone of this ketone crystallized from butyl acetate in needles of m.p. 274–275°.

Anal. Calcd. for $C_{21}H_{15}FN_4O_4$: C, 62.1; H, 3.7. Found: C, 62.3; H, 3.5.

Jerusalem, Israel

[Contribution from the Department of Chemistry, Purdue University]

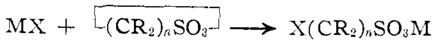
The Chemistry of Sultones. II. Alkylations of Organometallic and Related Compounds by Sultones[1]

By William E. Truce and Fred D. Hoerger[2]

Received October 1, 1954

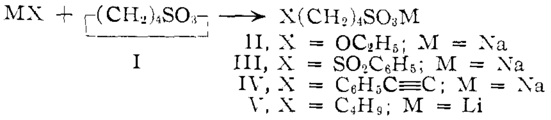
Sodium ethoxide, sodium benzenesulfinate, phenylethynylsodium, *n*-butyllithium and the sodium derivatives of diethyl malonate, ethyl acetoacetate and dibenzoylmethane are alkylated readily by 4-hydroxy-1-butanesulfonic acid sultone. The reaction of 4-hydroxy-1-butanesulfonic acid sultone with phenylmagnesium bromide produces both magnesium 4-phenyl-1-butanesulfonate and magnesium 4-bromo-1-butanesulfonate. The reaction of 2-*o*-hydroxyphenylethanesulfonic acid sultone with phenylmagnesium bromide gives *o*-(β-phenylsulfonylethyl)-phenol.

Helberger and co-workers[3,4] have shown recently that sultones serve as alkylating agents for a variety of nucleophilic reagents, such as alcohols, alkoxides, salts of inorganic and organic acids, amines and the sodium derivative of fluorene. The products of these reactions are substituted alkanesulfonates, but their structures were not established; presumably they arise according to the equation



$$MX + \overline{(CR_2)_nSO_3} \longrightarrow X(CR_2)_nSO_3M$$

In order to establish definitely the nature of the products obtained from the reactions of sultones with nucleophilic reagents, the reactions of sodium benzenesulfinate and sodium ethoxide with 4-hydroxy-1-butanesulfonic acid sultone (I) were studied. With sodium ethoxide, a 91% yield of sodium 4-ethoxy-1-butanesulfonate (II) was obtained. This product was characterized by comparison of its *p*-chloro-S-benzylthiuronium salt with an independently synthesized specimen. The independent synthesis involved the reaction of 4-chloro-1-ethoxybutane with aqueous sodium sulfite. The reaction of sodium benzenesulfinate with I gave a 53% yield of sodium 4-phenylsulfonyl-1-butanesulfonate (III). The S-benzylthiuronium derivative of III was identical with the corresponding derivative of a sulfonate independently synthesized from 4-chloro-1-phenylsulfonylbutane and sodium sulfite. These reactions confirm the structures assigned by Helberger to the alkylation products of sultones and establish a similarity in the reactions of sultones and alkyl sulfonates with nucleophilic reagents.



$$MX + \underset{\text{I}}{\underline{(CH_2)_4SO_3}} \longrightarrow X(CH_2)_4SO_3M$$

II, X = OC_2H_5; M = Na

III, X = $SO_2C_6H_5$; M = Na

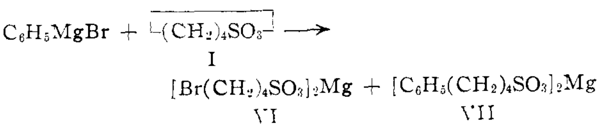
IV, X = $C_6H_5C{\equiv}C$; M = Na

V, X = C_4H_9; M = Li

In the first paper of this series[5] it was shown that C-alkylations are accomplished readily by the use of sultones as alkylating agents in the Friedel–Crafts reaction. Since alkyl sulfonates serve as carbon–carbon alkylating agents for organometallic compounds and since the reactions of sultones with nucleophilic reagents closely resemble the reactions of alkyl sulfonates, it seemed probable that sultones could serve as alkylating agents for carbon–carbon alkylations of organometallic and related compounds.

Carbon–carbon alkylation occurred readily in the reactions of both phenylethynylsodium and *n*-butyllithium with 4-hydroxy-1-butanesulfonic acid sultone (I). With phenylethynylsodium, an 85% yield of crude sodium 6-phenyl-5-hexyne-1-sulfonate (IV) was obtained; purification, however, reduced the yield to about 50%. The structure of IV was established by analysis of its *p*-chloro-S-benzylthiuronium derivative and by catalytic reduction to sodium 6-phenyl-1-hexanesulfonate. The latter compound was synthesized independently from 6-phenyl-1-bromobutane and sodium sulfite. The reaction of *n*-butyllithium with I gave a 58% yield of the very hygroscopic lithium 1-octanesulfonate which was characterized by comparison of its *p*-chloro-S-benzylthiuronium salt with an independently synthesized specimen.

The reaction of phenylmagnesium bromide with 4-hydroxy-1-butanesulfonic acid sultone produced a mixture of sulfonates, magnesium 4-bromo-1-butanesulfonate (VI) and magnesium 4-phenyl-1-butanesulfonate (VII). When two moles of the sultone I and one mole of Grignard reagent were employed,



$$C_6H_5MgBr + \underset{\text{I}}{\overline{(CH_2)_4SO_3}} \longrightarrow \underset{\text{VI}}{[Br(CH_2)_4SO_3]_2Mg} + \underset{\text{VII}}{[C_6H_5(CH_2)_4SO_3]_2Mg}$$

$$\text{VI} \xrightarrow[\text{2, HCl}]{\text{1, }Na_2CO_3} Br(CH_2)_4SO_3H \xrightarrow[-HBr]{} \text{I} \xrightarrow{MgBr_2} \text{VI}$$

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[1] Abstracted from a portion of the Ph.D. Dissertation of F. D. Hoerger, Purdue University, 1955.

[2] National Science Foundation Predoctoral Fellow, 1953–1954.

[3] J. H. Helberger, *et al.*, *Ann.*, **565**, 22 (1949); **562**, 23 (1949); **586**, 147 (1954); **586**, 158 (1954).

[4] J. H. Helberger, *Reichsamt Wirtschaftaufbau Chem. Br. Pruf. Nr.*, **15** (U. S. Office of Publication Board, P. B. 52013) 269 (1942).

[5] W. E. Truce and F. D. Hoerger, This Journal, **76**, 5357 (1954).