stirred an additional 1.5 hr. at room temperature, washed thoroughly with water, and the crude product (150 g.) was separated, dried over Drierite, and fractionated to give 122 g. of material with boiling range 61–67° (14 mm.). An analytical sample was shown by a vapor phase chromatogram to contain one major and three minor components. The major component has been assigned the structure $CF_2BrCH_2CH(OC_2H_5)_2$ (XVII) on the basis of n.m.r. spectra for hydrogen and fluorine.

An infrared spectrum showed two strong, broad absorption peaks in the 9.0–9.5-μ region and no absorption in the carbonyl or carbon–carbon double bond regions. Conversion was approximately 75%.

In a similar manner III, $CF_2BrCFClCH_2CHBrOC_2H_5$, reacted with ethanol to give XVIII, $CF_2BrCFClCH_2CH(OC_2H_5)_2$. N.m.r. spectra for hydrogen and fluorine were consistent with the assigned structure.

Reaction of V with Trifluoroethanol.—Trifluoroethanol (100 ml.) and 58 g. (0.17 mole) of $CF_2BrCH_2CHBrOCH_2CF_3$ were combined and stirred at room temperature with slow evolution of heat for 16 hr. and at 75° for 6 hr. White fumes were evolved and the flask was etched, indicating elimination of hydrogen fluoride. After work-up and fractionation of the crude material, a center cut showed both carbonyl and carbon–carbon double bond absorption in its infrared spectrum.

The desired acetal was successfully prepared in the following manner. Trifluoroethanol (200 ml.) and 84 g. (0.25 mole) of the subject ether were combined and stirred for 48 hr. at room temperature. During this period, the flask was swept with nitrogen and was backed by a cold trap. The solution was washed with water, and the crude material (64 g.) was dried over Drierite and fractionated to give 17.5 g. (21% conversion) of $CF_2BrCH_2CH(OCH_2CF_3)_2$ (XIX).

An infrared spectrum showed a strong, broad peak from 8.9-9.3 μ. No carbonyl or carbon–carbon double bond absorption was observed.

Trifluoroethanol also reacted with VI, $CF_2BrCFClCH_2CHBrOCH_2CF_3$, to give the corresponding acetal XX.

Reaction of II with Methylmagnesium Bromide.—$CF_2BrCH_2CHBrOC_2H_5$ was prepared from 2.84 moles of vinyl ethyl ether and excess CF_2Br_2 and was used without distillation. The crude ether was placed in a three-necked flask fitted with an addition funnel, stirrer, and condenser and was cooled to 0°. Two moles of methylmagnesium bromide in ethyl ether was then added dropwise over a 1-hr. period. The reaction was very vigorous and necessitated continued cooling. After addition was complete, the mixture was stirred for 1 hr. at 0° and for 4 hr. at room temperature. The mixture was filtered, and the organic layer was separated, dried, and fractionated to give 80 g. (19% conversion based on the vinyl ethyl ether) of $CF_2BrCH_2CH(CH_3)OC_2H_5$ (XXI). An infrared spectrum showed no carbonyl or carbon–carbon double bond absorption.

Reaction of Trifluoroethanol with Methylacetylene.—An autoclave was charged with 200 g. (2.0 moles) of trifluoroethanol, 80 g. (2.0 moles) of methylacetylene, and 10 g. of potassium hydroxide and was heated at 225° for 18 hr. Unchanged methylacetylene (65 g.) was bled into a trap, and the remainder was fractionated to give 17 g. of material, b.p. 57–72°. A vapor phase chromatogram showed that this fraction consisted of three components, the major one being trifluoroethanol. The material was washed thoroughly with water, and the organic layer was separated, dried, and fractionated to give 1 g. of material, identified as $(CH_3)_2C(OCH_2CF_3)_2$.

N.m.r. spectra of hydrogen and fluorine were consistent with the proposed structure. Conversion, based on chromatographic analysis of the 57–72° cut, was approximately 10%.

Reaction of $CCl_3CH_2CH_2OC_2H_5$ with Ethanolic Potassium Hydroxide.—A solution of 80 g. (1.2 moles) of potassium hydroxide in 200 ml. of 95% ethanol was heated to reflux followed by the dropwise addition of 70 g. (0.37 mole) of $CCl_3CH_2CH_2OC_2H_5$. The mixture was stirred at reflux for 20 hr., decanted, and washed with water. The insoluble organic layer was separated, dried, and fractionated to give a single product, b.p. 66° (17 mm.); $n^{23}D$ 1.4059; d^{23} 0.960; MRD calcd. for $C_2H_5OOCCH_2CH_2OC_2H_5$, 37.82; MRD found, 37.48. Physical constants reported for ethyl β-ethoxy propionate are b.p. 67° (17 mm.), $n^{25}D$ 1.4070, d^{25} 0.949.

An infrared spectrogram was identical with that of an authentic sample.

Preparation of Vinyl 2,2,2-Trifluoroethyl Ether.—A solution of 50 g. of potassium hydroxide in 300 g. (3.0 moles) of trifluoroethanol was sealed in a 1.4-l. stainless steel autoclave, which was then charged with acetylene to a pressure of 300 p.s.i.g. The autoclave was heated with rocking at 135° for 5 hr. and at 150° for 5 hr. Distillation of the product mixture gave the desired ether, b.p. 40–42°, in approximately 90% conversion.

Acknowledgment.—We wish to thank the U. S. Army Natick Laboratories for funds for the support of this research under Contract DA-19-129-QM-500 with Dr. J. C. Montermoso as project officer. Nuclear magnetic resonance spectra were obtained and interpreted by Dr. Wallace S. Brey, Jr., Department of Chemistry, University of Florida, Gainesville, Florida.

Fluoro Compounds. II.[1] Reactions and Nuclear Magnetic Resonance Studies of Some Fluorobromo Esters

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Fluorobromination of several α,β-unsaturated esters has been carried out using hydrofluoric acid and N-bromoacetamide. In each case the fluorine atom appeared on the β-carbon and was more easily lost than the α-bromine substituent in reaction with potassium phthalimide. Proton and fluorine nuclear magnetic resonance studies were made on several fluorobromo compounds. The fluorobromo compound derived from dialkyl maleate has been assigned the *threo* configuration; the corresponding fumarate derivative has been assigned the *erythro* configuration. At higher temperatures these two fluorobromo derivatives undergo interconversion. Electron paramagnetic resonance data and deuterium-exchange experiments do not indicate either a free radical or a carbanion intermediate for this interconversion.

In recent years there has been considerable interest in fluorinated compounds, particularly as potential antimetabolites. Some time ago we undertook a project on the synthesis of α-fluoro-β-alanine,[2,3] fluoroaspartic acid, and other fluoroamino acids. A possible intermediate in the synthesis of α-fluoro-β-alanine appeared to be β-bromo-α-fluoropropionic ester. Henne and Fox[4] tentatively assigned such a structure for the product obtained from ethyl dibromopropionate by halogen

(1) Part I: A. K. Bose, K. G. Das, and T. M. Jacob, *Chem. Ind.* (London), 452 (1963).

(2) Recently isolated as a metabolic product of 5-fluorouracil: C. Heidelberger and K. L. Mukherjee, *J. Biol. Chem.*, **235**, 433 (1960).

(3) Synthesized by E. D. Bergmann and S. Cohen, *J. Chem. Soc.*, 4669 (1961).

(4) A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.*, **76**, 479 (1954)

TABLE I

FLUOROBROMO ESTERS

Fluorobromo ester	B.p., °C. (mm.)	Yield, %	$n^{22}D$	Analysis, %
$CH_2FCHBrCOOCH_3$ (I)	70–72 (10)	50	1.4464	Calcd.: C, 25.94; H, 3.24; F, 10.27; Br, 43.24 Found: C, 25.83; H, 3.21; F, 10.16; Br, 43.36
$C_6H_5CHFCHBrCOOC_2H_5$ (II)	110–112 (1)	60	1.5125	Calcd.: C, 48.00; H, 4.36; F, 6.90; Br, 29.09 Found: C, 47.85; H, 4.36; F, 6.75; Br, 28.99
$CH_3OOCCHFCHBrCOOCH_3$ (III) (from dimethyl maleate)	108–110 (1)	55	1.4575	Calcd.: C, 29.63; H, 3.29; F, 7.81; Br, 32.92 Found: C, 30.26; H, 3.53; F, 7.73; Br, 32.59
$CH_3OOCCHFCHBrCOOCH_3$ (IV) (from dimethyl fumarate)	105–107 (1)	58	1.4580	Calcd.: C, 29.63; H, 3.29; F, 7.81; Br, 32.92 Found: C, 30.09; H, 3.47; F, 7.78; Br, 32.80
$C_2H_5OOCCHFCHBrCOOC_2H_5$ (V) (from diethyl maleate)	102–104 (1)	51	1.4550	Calcd.: C, 35.42; H, 4.43; F, 7.01; Br, 29.52 Found: C, 35.71; H, 4.58; F, 6.78; Br, 29.45
$C_2H_5OOCCHFCHBrCOOC_2H_5$ (VI) (from diethyl fumarate)	100–102 (1)	55	1.4550	Found to be homogeneous by gas chromatography and n.m.r. spectroscopy

exchange. In a previous communication[1] we have shown that this compound is actually β-fluoro-α-bromopropionic ester and is, therefore, unsuitable as an intermediate for the synthesis of α-fluoro-β-alanine.[5]

Recently a new method[6] has been described for the fluorobromination of alkenes. We have used this method for preparing fluorobromo esters of several unsaturated esters and have attempted to replace the bromine with the phthalimido function to obtain fluoroamino acid derivatives. An added interest in these compounds arose from the fact that several of the fluorobromo derivatives could possibly have restricted rotation and show the phenomenon of rotational isomerism.[7]

Experimental

A. Fluorobromination. General Procedure.—A solution of 0.05 mole of the α,β-unsaturated ester in 50 ml. of a 1:1 mixture of dry tetrahydrofuran and dry dichloromethane was cooled to −80° in a polyethylene container. A solution of 2.5 moles of anhydrous hydrogen fluoride in 50 ml. of a 1:1 mixture of tetrahydrofuran and dichloromethane prepared at −80° was added, followed by the addition of 0.065 mole of N-bromoacetamide which was previously purified by vacuum desiccation to remove all free bromine. The mixture was stirred for 1 hr. at −80° and left at 0° for 18 hr.[6] A reddish brown solution was obtained, which was poured into an excess of 10% cold sodium carbonate solution. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (20 ml.). The combined dichloromethane extract was washed with water (three 75-ml. portions) until neutral and dried over anhydrous magnesium sulfate; the solvent was removed under reduced pressure. The crude product (yield 55–70%) was purified by fractional distillation through a Vigreux column under reduced pressure. Old samples of N-bromoacetamide containing free bromine did not fluorobrominate in the presence of anhydrous hydrogen fluoride. After vacuum desiccation these samples were found to be good for the reaction.

The following α,β-unsaturated esters were fluorobrominated by the above procedure: (i) methyl acrylate, (ii) ethyl cinnamate, (iii) dimethyl maleate, (iv) dimethyl fumarate, (v) diethyl maleate, and (vi) diethyl fumarate. All the fluorobromo derivatives were characterized by gas chromatography and nuclear magnetic resonance spectra (see Table I). Fluorobromination of maleic anhydride failed.

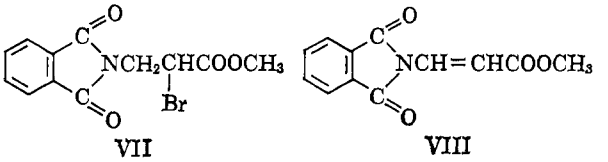
B. Some Reactions of Fluorobromo Esters. Action of Potassium Phthalimide on the Fluorobromo Derivatives of Ethyl Cinnamate (II).—A solution of the fluorobromo ester II (2.5 g.) in 20 ml. of anhydrous N,N-dimethylformamide or in 20 ml. of N,N-dimethylacetamide was stirred with dry powdered potassium phthalimide (1.8 g.) at room temperature for 2 days or at 70° for 1 hr. The reaction mixture was poured into 100 ml. of water. Phthalimide was quantitatively recovered.

The carbon tetrachloride layer was separated from the rest of the filtrate washed repeatedly with water, and dried over anhydrous sodium sulfate; the solvent was removed under reduced pressure. The liquid so obtained (1.9 g.) was purified by distillation under reduced pressure. This product was identified as ethyl α-bromocinnamate by comparison with an authentic sample[8,9] [identical retention time on a gas chromatography column (Perkin-Elmer "K" column) and identical n.m.r. spectra]. The corresponding acids[8,9] had the sample melting point and mixture melting point (131–132°).

Reaction between Methyl Fluorobromopropionate (I) and Potassium Phthalimide.—Methyl fluorobromopropionate reacted with potassium phthalimide in N,N-dimethylformamide at 70° to give a 70% yield of phthalimido ester free from fluorine. It was obtained as colorless crystals from methanol and had m.p. 91–95°.

Anal. Found: C, 50.54; H, 3.71; N, 5.08; Br, 19.44; F, 0.00.

This crystalline product was found to be a mixture of methyl α-bromo-β-phthalimidopropionate (VII) and methyl β-phthalimidoacrylate (VIII). The former was separated by chromatography over a Florosil column and identified with an authentic sample[10,11] by direct comparison and infrared spectroscopy. The acrylate derivative could not be isolated in analytically pure form; the infrared spectrum, however, indicated VII to be the contaminant.



VII VIII

Methyl α,β-dibromopropionate (2.46 g.) in 16 ml. of N,N-dimethylacetamide was stirred with potassium phthalimide (1.85 g.) for 4 days. The mixture was poured into ice water–chloroform. From the chloroform layer phthalimide (identified by melting point and infrared spectrum) was isolated (1.3 g.). Extraction of the water layer with chloroform gave 22 mg. of methyl α-bromo-β-phthalimidopropionate, m.p. 103.5–105°, which was identified by comparison with an authentic sample.[10,11]

Action of Potassium Phthalimide on Methyl Bromofluorosuccinate (III).—Methyl α-bromo-β-fluorosuccinate reacted with potassium phthalimide in N,N-dimethylformamide at 70° to give quantitative yields of phthalimide and a liquid product which contained much bromine and little fluorine.

Anal. Found: C, 45.47; H, 5.35; Br, 17.39; F, 2.05.

C. N.m.r. Studies on Fluorobromo Esters.—All the proton spectra were taken at 60 Mc. on a Varian Model DP-60 high resolution spectrometer using tetramethylsilane as an internal standard. Esters purified by repeated fractional distillation were

(5) Also see V. Tolman and K. Veres, *Collection Czech. Chem. Comm.*, **28**, 421 (1963).

(6) A. Bowers, *J. Am. Chem. Soc.*, **81**, 4107 (1959); C. H. Robinson, L. Finckenor, D. Gould, and E. P. Oliveto, *ibid.*, **81**, 2191 (1959).

(7) For example, see (a) P. M. Nair and J. D. Roberts, *ibid.*, **79**, 4565 (1957); (b) H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

(8) L. Suprin, *Ann. Chem.*, [12]**6**, 294 (1951).

(9) C. F. H. Allen and C. O. Edens, Jr., *Org. Syn.*, **25**, 92 (1949).

(10) S. Gabriel, *Chem. Ber.*, **41**, 242 (1908).

(11) A. Schöbert and H. Braun, *Ann. Chem.*, **542**, 274 (1939).

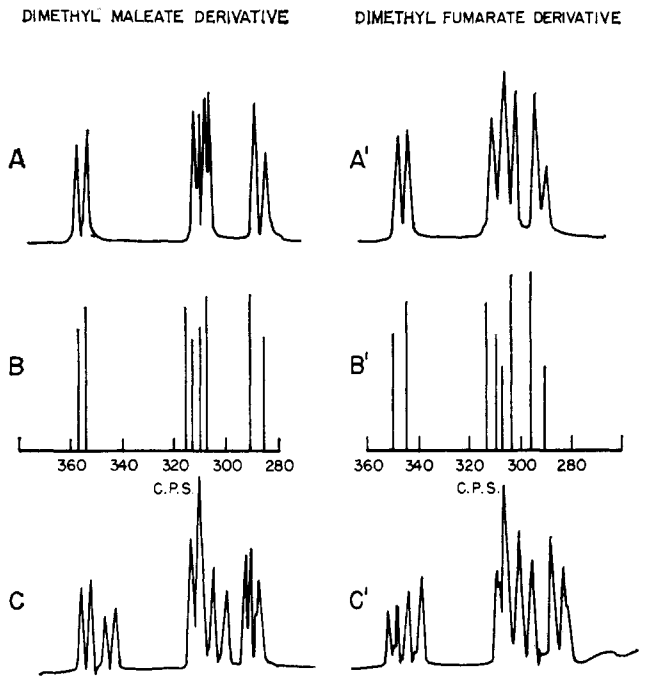


Fig. 1.—Proton nuclear magnetic resonance spectra: A and A′, observed spectra at room temperature; B and B′, calculated spectra; C and C′, observed spectra upon heating the sample for 5 hr. at 150°.

placed in n.m.r. tubes which were then evacuated at room temperature and sealed. The fluorine spectra were obtained on the same instrument at 56.4 Mc., but no internal standard was used. All the systems which were studied were of the ABX type and were analyzed according to the procedure described by Pople, Schneider, and Bernstein.[12]

The coupling constants and chemical shifts reported in Table II were assigned on the basis of line positions as well as relative intensities with the assumption that the coupling constants are positive.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR PROTON NUCLEAR MAGNETIC RESONANCE SPECTRA

No.	Fluorobromo derivative of	Chemical shifts, c.p.s.	Coupling constants, c.p.s.
1	Dimethyl maleate	ν_H = 333.19	$J_{FH\ (gem)}$ = 45.99
		$\nu_{H'}$ = 300.00	$J_{HH'}$ = 3.66
			$J_{FH'}$ = 23.69
2	Dimethyl fumarate	ν_H = 324.65	
		$\nu_{H'}$ = 298.55	$J_{FH\ (gem)}$ = 45.95
			$J_{HH'}$ = 4.62
			$J_{FH'}$ = 18.45
3	Diethyl maleate	ν_H = 328.36	$J_{FH\ (gem)}$ = 46.76
		$\nu_{H'}$ = 295.18	$J_{HH'}$ = 4.21
			$J_{FH'}$ = 23.44
4	Diethyl fumarate	ν_H = 320.06	$J_{FH\ (gem)}$ = 46.54
		$\nu_{H'}$ = 293.12	$J_{HH'}$ = 5.01
			$J_{FH'}$ = 17.50
5	Ethyl cinnamate	ν_H = 351.40	$J_{FH\ (gem)}$ = 45.61
		$\nu_{H'}$ = 275.00	J_{HH} = 9.38
			$J_{FH'}$ = 17.47

In the case of the dimethyl maleate derivative when the n.m.r. spectrum was run on the pure liquid, there was overlapping of peaks in the ABX portion of the spectrum. When, however, the spectrum was run in carbon tetrachloride solution, there was a clear separation between the sets of peaks, and assignment of transitions was possible without ambiguity. The assignments

(12) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 133.

TABLE III

FREQUENCIES IN CYCLES PER SECOND

Transition no.	Pure dimethyl maleate derivative (III)	Transition no.	Pure dimethyl fumarate derivative (IV)
8	358.75	8	350.17
6	355.12	6	345.59
7	313.45	4	309.94
4	312.20	2	305.39
5	309.79	7	304.43
2	308.51	5	299.81
3	289.02	3	291.32
1	285.35	1	286.64

to the different transitions, in accordance with the notation of Pople, Bernstein, and Schneider,[12] are shown in Fig. 1 and listed in Table III.

Temperature Studies on Fluorobromo Derivatives of Dimethyl Maleate and Dimethyl Fumarate.—A sample of freshly distilled fluorobromo ester (sealed in an n.m.r. tube as described above) was heated in a constant temperature bath at 150 ± 0.5° for about 30 min. After rapidly cooling the tube to room temperature, the spectrum was recorded. The sample was again heated at 150° for different periods (aggregating more than 5 hr.). New peaks (see Fig. 1) appeared, the intensities of which were found to increase with time; it was also noticed that only very little of the sample decomposed. This decomposition, however, did not interfere with the portion of the spectrum under study.

This experimental procedure was repeated using a freshly distilled sample of fluorobromo derivative of dimethyl fumarate. Again we observed the formation of new peaks the intensities of which increased with time (see Fig. 1).

We were able to identify the new peaks obtained in the spectrum of the dimethyl maleate derivative after heating as those of the dimethyl fumarate derivative. Similarly, the new peaks which appeared in the spectrum of dimethyl fumarate derivative after heating were identified with the frequencies of the dimethyl maleate derivative.

Similar results were obtained from the diethyl maleate and fumarate derivatives. These liquid samples had to be heated to 170° in order to have any appreciable change. In similar experiments with the fluorobromo derivative of ethyl cinnamate, extensive decomposition of the ester was found with etching of glass due to loss of hydrogen fluoride in preference to hydrogen bromide. The decomposition product was purified by short-path distillation and was identified as mainly α-bromocinnamate by n.m.r. spectrum and by comparison with an authentic sample.[8]

Fluorine Spectra.—The coupling constants obtained from the proton n.m.r. spectrum and the fluorine n.m.r. spectrum were in agreement. The fluorine spectrum was also used for studying the effect of temperature on the fluorobromo derivatives of maleates and fumarates, and results similar to those from the proton n.m.r. spectra were obtained.

Discussion

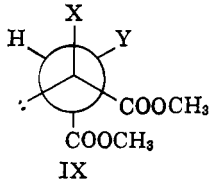
Orientation and Relative Reactivities of the Halogen Atoms in Fluorobromo Esters. A. Orientation.—The fluorobromination of acrylate and cinnamate esters was found to be a specific reaction leading to a single product as was evident from vapor phase chromatography and n.m.r. spectra. The appearance of the fluorine on the carbon atom β to the carboxyl group is to be expected on the basis of higher electronegativity of fluorine than that of bromine. During fluorobromination appreciable quantities of the maleate ester were converted into fumarate esters which remained mostly unchanged in the course of the halogenation.

B. Reactivity.—Methyl β-fluoro-α-bromopropionate reacted with potassium phthalimide in N,N-dimethylformamide or N,N-dimethylacetamide at room temperature for 2 days or at 70° for 1 hr. to give about 70% yield of the phthalimido ester. Methyl dibromopropionate and several other fluorobromo esters, how-

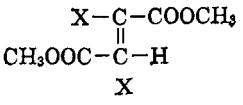
ever, gave phthalimide and the corresponding unsaturated α-bromo esters in high yield; contrary to expectation, the phthalimido ester was formed only in small quantities.

It is of interest to note that in the dehydrohalogenation of dimethyl maleate derivative in the presence of potassium phthalimide the product was a mixture of unsaturated bromo esters and fluoro esters. A quantitative analysis of this mixture was conveniently carried out by studying the n.m.r. spectrum of the total product. The vinyl protons in the bromo esters appeared as single peaks, whereas the vinyl protons of the unsaturated fluoro esters appeared as doublets. It was assumed that the doublet with the larger coupling constant (9.94 c.p.s.) corresponded to the *trans* ester. The *cis* ester showed the coupling constant of 3.14 c.p.s. It was estimated that the four unsaturated halo esters were present in the following approximate proportions: bromomaleate, 25%; bromofumarate, 36%; fluoromaleate, 16%; fluorofumarate, 23%.

In all probability the dehydrohalogenation is an ionic reaction. If it is a concerted process without involving a carbanion, then the molecule may have to arrange itself in conformation IX so that the two leaving groups and the carbons involved will all be in one plane, and the *trans* ester X will be favored. The

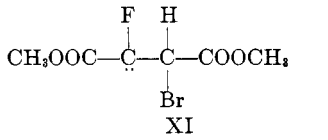


IX

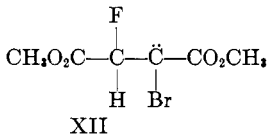


conventional reaction mechanism involving a carbanion would also favor the formation of the *trans* ester X. We have noted that the fluorobromo derivative from dimethyl melate produces more *trans* than *cis* ester in its reaction with potassium phthalimide. This would indicate the *threo* configuration for the starting fluorobromo ester. The same conclusion has been arrived at from a consideration of the stereochemistry of the addition of halogen to unsaturated compounds (see below).

In view of Bergmann's[13] work the formation of carbanion XI should be easier than the alternative carbanion XII. It might, therefore, be expected that the



XI

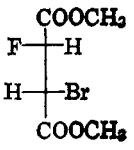


XII

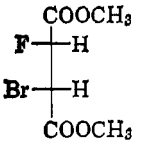
unsaturated fluoro ester would be formed in preference to the bromo ester. This is, however, contrary to our finding that the proportion of the bromo ester to the fluoro ester is 3:2.

In this connection it is interesting to note that Viehe, *et al.*,[14] have reported preferential loss of hydrogen bromide from bromofluoroethylene but hydrogen fluoride from chlorofluoroethylene on treatment with sodium amide.

Fluorobromo Derivatives of Dimethyl Maleate and Dimethyl Fumarate.—In general, the addition of bromine or chlorine to a double bond takes place in a *trans* fashion. Thus, the bromination of maleic and fumaric acids has been reported to lead to *meso*- and *dl*-α,α'-dibromosuccinic acids,[15] respectively. According to Terry and Eichelberger,[16] however, the salts of these acids add bromine both in the *trans* and *cis* manner. The stereochemistry of bromofluorination with hydrofluoric acid and N-bromoacetamide also appears to follow a *trans* course in steroids.[5,6] Assuming *trans* addition, one can assign the *threo* (III) and *erythro* (IV) configurations to the fluorobromo derivatives from dimethyl maleate and fumarate, respectively. Most probably both isomers can be expected to consist of rapidly interconverting mixtures of rotamers.



III



IV

Recently Bothner-By and Naar-Colin[17] and Anet[18] have studied the n.m.r. spectra of several symmetrical 2,3-disubstituted butanes. They have reported that the $J_{AA'}$ is higher in the *meso* isomer than in the *dl* isomer for the dibromo, the dichloro, and diphenyl derivatives. The diacetoxy butanes, however, are an exception to this pattern. Inspection of Table II shows that the fluorobromo derivative of a dialkyl fumarate (*erythro* configuration) has a higher $J_{AA'}$ than the corresponding maleate (*threo* configuration).

Bothner-By and Naar-Colin[17] and also Anet[18] have estimated the population of the three chief rotamers for both the *meso* and *dl* types of 2,3-disubstituted butanes on the basis of the assumptions that the rotamer, in which the methine protons are *trans*, has a large coupling constant, and the two gauche forms have small and equal coupling constants.

The $J_{AA'}$ values for the maleate and fumarate derivatives resemble the values reported for 2,3-diacetoxybutanes (*meso* isomer, 3.53 c.p.s.; *dl* isomer, 5.12 c.p.s.).[17] To rationalize the low value of $J_{AA'}$ for the *dl* isomer, Bothner-By and Naar-Colin have suggested mutual attraction of the two acetoxy groups. In the case of the fluorobromo derivative from fumaric ester, however, similar attraction is implausible. It is likely that the coupling constants and the equation used for estimating the relative contribution of rotamers are not valid—at least for the fluorobromo compounds.

It is interesting to note here that the replacement of the methyl ester group by an ethyl ester group changes the coupling constant noticeably (see Table II).

Gutowsky, Belford, and McMahon[7b] have studied 2,3-disubstituted butane systems by measuring the effect of temperature on $J_{AA'}$. In our own study we have found $J_{AA'}$ to be temperature dependent. (For the diethyl maleate derivative (III), $J_{HH'} = 4.21$ c.p.s. at room temperature and 4.70 c.p.s. at 102°.)

The study of the effect of temperature on the n.m.r. spectra of the fluorobromo derivatives established that a reversible interconversion of the *threo* and *erythro* iso-

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mers of 2-fluoro-3-bromosuccinic acid esters takes place at higher temperatures. Such interconversion must involve the scission of a chemical bond and its regeneration in a different steric fashion.

Fluorine has been found to be an activating group. Bergmann[18] has shown that, on treatment with a base, fluoroacetic esters readily produce carbanions which can be alkylated. In view of this it appeared plausible that carbanion IX might be instrumental in the interconversion of the *threo* and *erythro* isomers. To test this possibility a sample of the dimethyl fumarate derivative and deuterated methanol (CH_3OD) was heated to 150–155° for 2 hr. The n.m.r. spectrum indicated the usual conversion of the *erythro* to the *threo* isomer, but no deuterium incorporation. It is evident, therefore, that a carbanion is not involved in the isomer interconversion. We have observed that hydrogen fluoride failed to add to bromomaleate and bromofumarate.

No etching of the n.m.r. tubes was observed during the heating experiments. Reversible elimination and addition of hydrogen fluoride is, therefore, unlikely to be involved in the interconversion of these esters.

A free-radical mechanism does not appear to be involved because e.p.r. spectra studies on the heated sample of the dimethyl maleate derivative failed to indicate any unpaired electrons. Moreover, if free radicals are formed, the n.m.r. spectrum at high temperature should have shown broadening of the peaks.[19] The proton n.m.r. peaks, however, were found to be sharp at all the temperatures studied. If, however, free radicals have very short life or are produced in small concentrations, our methods for the detection of free radicals may have been inadequate.

The mediation of a carbonium ion in the interconversion of the *threo* and the *erythro* epimers is possible. Further work will be necessary to get definitive evidence about the mechanism of interconversion of the isomeric fluorobromo esters.

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Reactions of N-Bromosuccinimide and Indoles. A Simple Synthesis of 3-Bromooxindoles[1]

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N-Bromosuccinimide (NBS) in *t*-butyl alcohol converts 3-alkylindoles such as skatole, indole-3-acetic acid, and other indole-3-alkanoic acids to the corresponding oxindoles when a 1:1 mole ratio of NBS to indole is used. 3-Bromooxindoles are obtained with a 2:1 ratio of reactants. Oxindoles are intermediates in the formation of 3-bromooxindoles, but NBS does not attack oxindoles in dry alcohol. The hydrogen bromide evolved in oxindole formation in the first step must catalyze the formation of 3-bromooxindoles, probably by way of the enol form of the oxindole. Basic catalysis of 3-bromination of oxindoles by NBS can be effected also, but in neutral aqueous *t*-butyl alcohol 5-bromooxindoles are formed. In glacial acetic acid NBS effects bromination of the indole hetero ring. The reaction of indoles and NBS is the method of choice for the synthesis of oxindole-3-acetic acid and related compounds, as well as oxindole analogs of tryptamine and tryptophan. The reaction also provides the first simple and general route to 3-alkyl-3-bromooxindoles, stable intermediates which undergo facile replacement of the halogen by alcohols, water, and other nucleophiles. The mechanisms of oxindole formation and bromination are discussed. The ultraviolet and infrared absorption spectra of the bromoindoles are tabulated.

Interest in the products of chemical and enzymatic oxidations of indoles[2] prompted us to seek new methods for the synthesis of oxindoles and dioxindoles related to indole-3-acetic acid (IAA). Lawson and Witkop have shown that N-bromosuccinimide (NBS) can be used to convert indoles to oxindoles[3,4] and have drawn attention to the importance of the solvent in determining the nature of the products—nonaqueous media favoring bromine substitution of the hetero ring, aqueous media supporting oxindole formation.[5]

In the course of further studies on the effects of solvents, we have found that NBS in *t*-butyl alcohol is an excellent system for converting a variety of 3-alkylindoles to the corresponding oxindoles in one operation. Depending on the NBS–indole ratio, either simple oxindoles or 3-bromooxindoles can be obtained (eq. 1). The latter compounds are stable but reactive intermediates accessible for the first time by a simple and convenient procedure. Some of their reactions will be described in a forthcoming publication.[6] We have also studied the reactions of NBS and a variety of indoles in glacial acetic acid, in which substitution predominates.

Reactions in *t*-Butyl Alcohol.—The reactions of NBS and indoles in *t*-butyl alcohol are summarized in Table I.

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