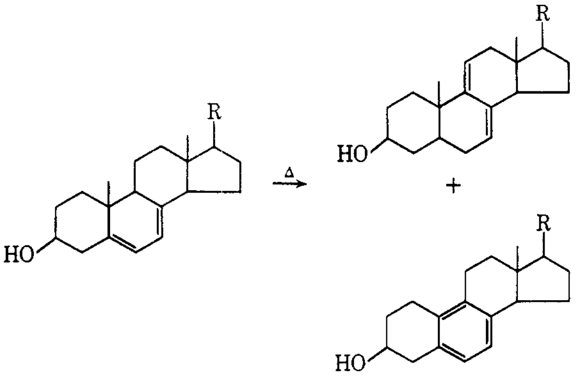
acterized further and various sterol mixtures as indicated by ultraviolet analysis. The sterol fractions were acetylated and chromatographed on silica gel to give a sterol with no absorption in the ultraviolet above 210 mμ which has not been identified and a mixture of ergosteryl acetate and another acetate, λ_{max} 242 and 250 mμ which was isolated in pure form by repeated recrystallization from acetone. The purified acetate exhibited mp 175–175.5°, λ_{max} 235, 242 and 251 mμ, and displayed infrared and nmr spectra identical with those of authentic ergosterol D acetate.[8] The identity was further confirmed by hydrolysis to the parent alcohol followed by spectral and thin layer chromatographic comparison with an authentic sample of ergosterol D.

A fourth acetate was isolated from later fractions and exhibited a singlet aromatic resonance at 6.85 ppm and was shown by infrared and nmr analyses, mixture melting point, and chromatographic behavior to be identical with neoergosteryl acetate.[9]



Evidence that neoergosterol was produced by a demethanation reaction was provided by the mass spectral identification of methane among the gases produced during the thermal reaction.

At 400° it was estimated that ergosterol D is the major component of the sterol mixture, while the amount of neoergosterol seems to increase at higher temperature.

The thermal isomerization of $\Delta^{5,7}$-dehydrocholesterol seemed to be slightly more complicated, but the major product was readily identified as cholesta-7,9(11)-dien-3β-ol.

It can now be claimed that isomerization routes to all the ergosterol isomers (B_1, B_2, B_3 and D) are available.

Experimental Section

Thermal Rearrangement of Ergosterol.—A 3.0-g sample of recrystallized ergosterol, mp 160–161°, was placed in a 50-ml, round-bottom flask equipped with a condenser and maintained under a nitrogen atmosphere. The flask was submerged in a Woods metal bath at 400 ±10° for 5 min. The yellow solid which resulted on cooling was dissolved in a minimal amount of benzene and applied to a column containing 300 g of neutral alumina. Elution with benzene and 10% ether–benzene gave four fractions: (a) 0.40 g which showed no absorption in the ultraviolet above 210 mμ; (b) 0.056 g of an oil; (c) 2.40 g of sterol mixture; and (d) 0.154 g, mp 160–161°, whose melting point was not depressed on admixture with ergosterol. The acetate of this fraction exhibited mp 170–172° and an infrared spectrum identical with that of authentic ergosteryl acetate.

Fraction c was kept with a large excess of acetic anhydride and a trace of pyridine for 24 hr. The volatile reactants were removed under diminished pressure and thin layer chromatography of the residue on silica gel G showed a minimum of three spots. A small portion was placed on a silica gel column and eluted with 12.5% benzene in pentane to give the following fractions. (a) A solid, mp 148–151°, no absorption in the ultraviolet above 220 mμ, which was not investigated further. (b) A solid, λ_{max} 242 mμ (ε 12,300), which after repeated recrystallization from acetone showed mp 175–175.5°, λ_{max} 235, 242, and 251 mμ (ε 12,800, 15,000, and 10,300, respectively). The melting point of this sample was not depressed on admixture with an authentic sample of ergosterol D acetate and its infrared spectrum proved to be identical with that of the authentic sample. Hydrolysis of the acetate afforded an alcohol: mp 164–165°; λ_{max} 235, 242 (16,300), and 251 mμ. This sample did not depress the melting point of an authentic sample of ergosterol D, and its infrared spectrum was identical with that of the authentic sample. (c) A solid which after recrystallization from ether–methanol showed mp 117–117.5°, $[\alpha]^{32}$ −6.5°, λ_{max} 269 and 278 mμ (ε 440), was obtained as the third fraction. This solid did not depress the melting point of an authentic sample of neoergosteryl acetate. This solid also showed the same R_f value as neoergosteryl acetate on thin layer chromatography. Hydrolysis with alkali afforded a solid, mp 152–153°, $[\alpha]^{28}$ −8.3°, λ_{max} 269 (435) and 278 mμ, whose nmr and infrared spectra were identical with those of an authentic sample of neoergosterol.

A similar separation of the sterol acetates was achieved using alumina, except in this instance neoergosteryl acetate eluted before ergosterol D acetate. It was estimated, by ultraviolet analysis of various chromatographic fractions, that fraction c contained 70–77% ergosterol D and 15–18% neoergosterol.

Thermal Rearrangement of 7-Dehydrocholesterol.—A 3.0-g sample of 7-dehydrocholesterol was heated at 400° for 5 min. Column chromatography using alumina gave five fractions: (a) 50 mg of oil showing no ultraviolet absorption; (b) 100 mg of oil which could not be crystallized; (c) 800 mg of solid, mp 102–110°, λ_{max} 235, 242 (ε 16,000), and 250 mμ (lit., for cholesta-7,9-(11)-dien-3β-ol, mp 107–110°,[10] λ_{max} 235, 243 (ε 16,100), and 251 mμ);[11] (d) 1.5 g of solid, mp 148–150°, whose infrared and ultraviolet spectra were identical with those of $\Delta^{5,7}$-dehydrocholesterol; and (e) 0.5 g of oil which was not characterized.

Registry No.—Ergosterol, 57-87-4; dehydrocholesterol, 434-16-12.

[8] We wish to express our appreciation to Dr. E. M. Chamberlin for making this sample available.

[9] We wish to express our appreciation to Dr. Y. Sato for making available a sample of neoergosterol.

(10) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953).

(11) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1891 (1951).

Kinetics of Bromination of Benzene and Methylbenzenes in Acetic and Trifluoroacetic Acids[1,2]

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As part of a general investigation of rapid halogenation reactions, kinetic studies of the bromination in water of aromatic amines,[3] of anisoles,[4] and of benzene

(1) Paper II in a series: Bromination of Polymethylbenzenes.

(2) Paper I: P. Alcais, F. Rothenberg, and J. E. Dubois, *J. Chim. Phys.*, 1443 (1966).

(3) (a) J. E. Dubois, P. Alcais, and G. Barbier, *Compt. Rend.*, **254**, 3000 (1962); (b) J. E. Dubois and R. Uzan, *Tetrahedron Letters*, 2397 (1964); (c) *ibid.*, 309 (1965); (d) J. E. Dubois, P. Alcais, and G. Barbier, *Bull. Soc. Chim. France*, in press.

(4) (a) J. E. Dubois and J. J. Aaron, *Compt. Rend.*, **258**, 2313 (1964); (b) *J. Chim. Phys.*, 1354 (1964).

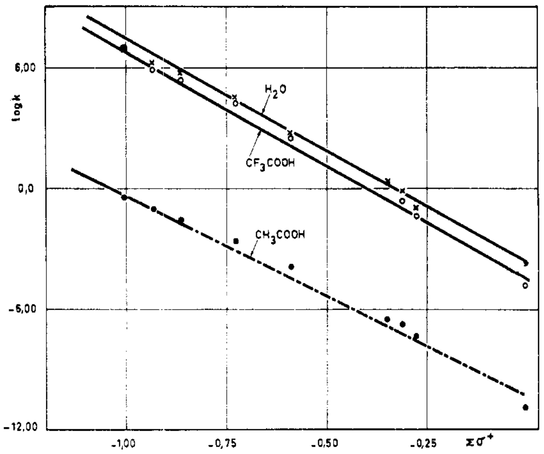


Figure 1.—Bromination of polymethylbenzenes (effect of substituents and solvents): $\sigma_0{}^{+\mathrm{Me}} = -0.276$ (C. W. McGary, Y. Okamoto, and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3037 (1955)); $\rho_{\mathrm{H_2O}} = -10.7$ (correlation coefficient = 0.998); $\rho_{\mathrm{CF_3COOH}} = -11.3$ (correlation coefficient = 0.995); $\rho_{\mathrm{CF_3COOH}} = -10.0$ (correlation coefficient = 0.995). The dotted part of correlation in CH_3COOH is extrapolated from H. C. Brown and L. M. Stock, *ibid.*, **79**, 1421 (1957).

and methylbenzenes[2] have been reported. This work has permitted the establishment of a scale of absolute reactivity for the bromination of benzene and substituted benzenes in water.[5]

The recent publication by Berliner and Gaskin,[6a] of rate constants for the bromination of benzene in water,[6b] prompts us to present our values for the bromination rates of benzene and polymethylbenzenes in acetic acid and trifluoroacetic acid. This work was undertaken in order to evaluate the respective influence of solvent on absolute rate constants and on structural effects as measured by the reaction ρ values.[7]

The results are presented in Table I for acetic and in Table II for trifluoroacetic acid. The results in Table I were obtained in the absence of added bromide ion but under the experimental conditions, the reaction was shown to be wholly second order. It was not possible to obtain the rate constants for the weakly substituted benzenes in acetic acid, but as shown in Table II the complete series from benzene to pentamethylbenzene was studied in trifluoroacetic acid.

The values given in Table II correspond to a constant bromide ion concentration and in trifluoroacetic acid it is not possible to separate the relative effects of Br_2 and Br_3^-, since the constant K for the tribromide dissociation is unknown in this medium. The tribromide ion can be considered as unreactive toward the polymethylbenzenes,[6a] and the real rates are related to given values by the constant factor $1/(K(\mathrm{Br}^-) + 1)$.

TABLE I

POLYSUBSTITUTED METHYLBENZENE BROMINATION IN ACETIC ACID

Aromatic substrate[a]	k[b]
1,3,5-Trimethylbenzene	4.00×10^{-2}
1,2,3,5-Tetramethylbenzene	9.50×10^{-2}
Pentamethylbenzene	3.50×10^{-1}

[a] The initial bromine concentration was chosen to have first order in reactant (10^{-4} mole l.$^{-1}$ < Br_2 < 6.10^{-4} mole l.$^{-1}$). Methylbenzene was kept in excess except for pentamethylbenzene. [b] All rate constants are in l. mole^{-1} min^{-1} at 25°; reproducibility ±5%, no added bromide.

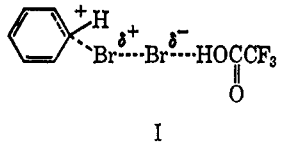
TABLE II

THE BROMINATION OF BENZENE AND METHYLBENZENES IN TRIFLUOROACETIC ACID

Aromatic substrate	Bromination site	Expt	Rate constants[a] relative to the bromination site	$k_{\mathrm{H_2O}}/k_{\mathrm{CF_3COOH}}$[b]
Benzene[c]	1	3	1.71×10^{-5}	9.35
Methylbenzene[c,d]	2	3	4.18×10^{-2}	2.65
	4	3	2.52×10^{-1}	2.7
1,3-Dimethylbenzene[d]	2	5	2.46×10^{2}	*e*
	4	5	3.70×10^{2}	1.3
1,3,5-Trimethylbenzene	2	13	2.10×10^{5}	2.4
1,2,4,5-Tetramethylbenzene	3	7	5.02×10^{2}	*f*
1,2,3,4-Tetramethylbenzene	5	3	1.87×10^{4}	1.4
1,2,3,5-Tetramethylbenzene	4	6	8.00×10^{5}	2.1
Pentamethylbenzene	6	15	5.75×10^{6}	0.92

[a] Constants are given in l. mole^{-1} min^{-1}; [LiBr] = 0.2 mole l.$^{-1}$; temperature = 25°; reproducibility ±5%. Constants in one site are determined by percentage of isomers (vpc) and are statistically corrected when there are many equivalent positions. [b] [LiBr] = 0.2 mole l.$^{-1}$ in CF_3COOH, [NaBr] = 0.2 mole l.$^{-1}$ in H_2O.[2] [c] These substrates have also been recently studied by H. C. Brown and R. A. Wirkkala, without lithium bromide added [R. A. Wirkkala and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 1447 (1966)]. [d] Rate constants calculated using the vpc analysis of products. [e] No such isomer has been found in the bromination in water. [f] Not included in the correlation.

The rate constants observed in trifluoroacetic acid are about 10^6 larger than those observed in acetic acid and are comparable to those in water.[2,6b] The large increase in rate constant in going from acetic acid to water can mostly be attributed to the corresponding increase in dielectric constant, $\epsilon_{25°}^{\mathrm{CH_3COOH}}$ 6.20 to $\epsilon_{25°}^{\mathrm{H_2O}}$ 78.54.[8] The same explanation cannot hold for the large rate constants observed in trifluoroacetic acid because the dielectric constant of this latter is only $\epsilon_{25°}^{\mathrm{CF_3COOH}}$ 8.45. It would appear that the increase in rate in trifluoroacetic acid is due to its polarity which gives rise to the specific solvation of the leaving bromide ion in the transition state (I).[9a]



$$C_6H_6{}^{+}H\cdots\overset{\delta+}{Br}\cdots\overset{\delta-}{Br}\cdots HOC(=O)CF_3$$

I

In addition, the resultant increase in polarization of the molecular bromine bond would lead to an increase

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(5) J. E. Dubois and J. P. Doucet, *Tetrahedron Letters*, 3413 (1967).

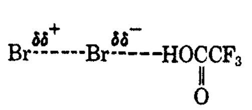
(6) (a) E. Berliner and F. Gaskin, *J. Org. Chem.*, **32**, 1660 (1967). (b) The value proposed by these authors ($k_{\mathrm{Br_2}} = 5.00 \times 10^{-3}$ l. mole^{-1} min^{-1}) corresponds to the value calculated with our results[2] [$k_{\mathrm{g}} = 9.6 \times 10^{-4}$ l. mole^{-1} min^{-1} or $k_{\mathrm{Br_2}} = k_{\mathrm{g}}[1 + K(\mathrm{Br}^-)] = 4.02 \times 10^{-3}$ l. mole^{-1} min^{-1}: F. Rothenberg, Thèse III° Cycle, Paris, 1966].

(7) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(8) It has been shown that in methanol–water mixtures the rate constant is related to the dielectric constant of the solvent system.[5] This would tend to establish a relationship between the dielectric constant and the reaction rate. The present results could be interpreted as evidence against this correlation and the argument does not preclude the possibility of other effects such as specific solvation.

(9) (a) R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **82**, 4547 (1960); (b) E. Berliner, *Progr. Phys. Chem.*, **2**, 253 (1964).

in the electrophilic nature of the halogenation reagent (II) thus modifying the structure of the intermediate



$$\overset{\delta\delta^+}{Br}\text{------}\overset{\delta\delta^-}{Br}\text{-----}HO\underset{\underset{O}{\|}}{C}CF_3$$

II

complex[9b] formed during the reaction with respect to those formed in acetic acid.

It has not been possible to obtain evidence uniquely in favor of either of these proposed effects but work is being carried in this direction.

When log k is plotted against $\Sigma\sigma^+$ (Figure 1) it is seen that the slopes of the correlation lines in the three solvents (water, trifluoroacetic acid, and acetic acid) are essentially the same even though the domains of absolute reactivity are quite different. It can be stated that the bromination of benzene and methylbenzenes is *isosensitive* to these solvents, the same structural correlations being obtained independent of thenat ure of the solvent.

Experimental Section

Preparation of Solvents and Reagents.—Commercial acetic acid (Prolabo) was distilled with a trace of bromine in the dark. Blank experiments showed that the acid obtained does not react with bromine in a noticeable quantity during the course of an experiment.

Commercial trifluoroacetic acid (Synthèse et Recherches) was distilled over phosphoric anhydride; lithium bromide (Prolabo R.P.) was dried at 180° for several days. Water could not be directly determined by the classical Karl Fischer method in this solvent because of the esterification of the methanol in the Karl Fischer reagent. Nevertheless by allowing the acid to react with an excess of dried pyridine (1 ml of acid with 10 ml of pyridine containing less than 100 mg/kg of water), water could be determined in the resultant salt solution. All acid fractions were then checked for dielectric constant and fractions outside the range 8.40–8.50 at 25° were not used, the water content being always less than 500 mg/kg.

Commercial substituted benzenes (K & K) and benzene (Prolabo Spectrograde) were purified by zone melting (solid products) or by preparative vapor phase chromatography (vpc). The purity of the liquid products was checked by vpc.

Measurement Methods and Experimental Results.—The rate constants were obtained by following the bromine concentration; two methods were used to cover the entire range of reactivity: (1) for highly reactive substrates, the couloamperometric method;[10] and (2) for the less reactive substrates a modification of the classical method of bromine determination by arsenic trioxide was used.

The reaction was shown to be first order with respect to each reagent. The reaction conditions were such that dibromination was insignificant, this being verified by vpc analysis of the reaction mixtures. The analytical samples were obtained by carbon tetrachloride extraction of the neutralized reaction mixtures.

For the case of toluene and m-xylene the two predominating monobromo products were identified by the comparison of the retention times with those of known products.

Registry No.—Benzene, 71-43-2; acetic acid, 64-19-7; trifluoroacetic acid, 76-05-1; methylbenzene, 108-88-3; 1,3-dimethylbenzene, 108-38-3; 1,3,5-trimethylbenzene, 108-67-8; 1,2,4,5-tetramethylbenzene, 95-93-2; 1,2,3,4-tetramethylbenzene, 488-23-3; 1,2,3,5-tetramethylbenzene, 527-53-7; pentamethylbenzene, 700-12-9.

(10) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

The Reaction of Isocyanic Acid with Trifluoroacetic Anhydride. Preparation of Trifluoroacetyl Isocyanate and 2,2,2,2′,2′,2′-Hexafluorodiacetamide

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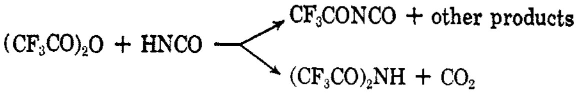
The reaction of isocyanic acid with trifluoroacetic anhydride (eq 1) has been found to be a useful method for the preparation of trifluoroacetyl isocyanate and 2,2,2,2′,2′,2′-hexafluorodiacetamide (perfluorodiacetamide). The relative yields of trifluoroacetyl isocyanate and perfluorodiacetamide are influenced by the reaction conditions. No successful reaction of isocyanic acid with a carboxylic acid anhydride appears to have been reported previously.[1–5]



$$(CF_3CO)_2O + HNCO \rightarrow \begin{cases} CF_3CONCO + \text{other products} \\ (CF_3CO)_2NH + CO_2 \end{cases} \qquad (1)$$

Trifluoroacetyl isocyanate was prepared by the reaction of isocyanic acid and trifluoroacetic anhydride in a 2:1 mole ratio, respectively. The reaction was run on a small scale without solvent. The isocyanate was separated from carbon dioxide and other byproducts by fractionation in a vacuum line. When a 1:1 mole ratio of reactants was used the isocyanate was formed, but could not be separated from trifluoroacetic anhydride and trifluoroacetic acid, which were present according to an infrared spectrum.

Trifluoroacetyl isocyanate, bp 35°, was characterized by its molecular weight of 142 (calcd: 139) and fluorine nmr and infrared spectra. The infrared spectrum showed absorptions caused by the asymmetric isocyanate stretching vibration at 2275 and 2235 and the symmetric stretching vibration at 1444 cm^{-1}.[6] The carbonyl absorption was observed at 1787 cm^{-1}. The fluorine nmr spectrum contained a single peak at 77.4 ppm from trichlorofluoromethane (solvent and internal standard), in the CF_3 region.[7,8]

While an excess of isocyanic acid was used for the preparation of trifluoroacetyl isocyanate, an excess of trifluoroacetic anhydride was used for the preparation of perfluorodiacetamide.[9] The reaction time was also longer. Perfluorodiacetamide was isolated in about 90% yield (based on isocyanic acid) by fractionation in

(1) Reactions of isocyanic acid with acid chlorides,[2,3] chlorides of phosphorus[2,3] and silicon,[2] trialkyltin oxides,[5] and trialkylantimony oxides[5] have been described elsewhere.

(2) P. R. Steyermark, *J. Org. Chem.*, **28**, 586 (1963).

(3) P. R. Steyermark, U. S. Patent 3,155,700 (1964).

(4) G. K. Weisse and R. M. Thomas, U. S. Patent 3,246,033 (1966).

(5) W. Stamm, *J. Org. Chem.*, **30**, 693 (1965).

(6) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 3428 (1956); H. Hoyer, *Ber.*, **89**, 2677 (1956).

(7) *Cf.* trifluoroacetic acid, which absorbs at 76.5 ppm under these conditions.[8]

(8) G. Filipovitch and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

(9) Perfluorodiacetamide has been prepared by several other methods: (a) G. H. Smith, U. S. Patent 2,701,814 (1955); (b) J. A. Young, W. S. Durrell, and R. D. Dresdner, *J. Am. Chem. Soc.*, **84**, 2105 (1962); (c) W. S. Durrell, J. A. Young, and R. D. Dresdner, *J. Org. Chem.*, **28**, 831 (1963); (d) T. J. Mao, R. D. Dresdner, and J. A. Young, *J. Inorg. Nucl. Chem.*, **24**, 53 (1962).