Journal of Fluorine Chemistry, 31 (1986) 151–174

Received: August 8, 1985; accepted: December 26, 1985

SOME APPROACHES TO THE SYNTHESIS OF FLUORINATED ALCOHOLS AND ESTERS. III. SYNTHESIS OF 2-(F-ALKYL)ETHANOLS FROM 2-(F-ALKYL)-1-IODOETHANES AND AMIDES.

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SUMMARY

1-Iodo-2-(F-alkyl)ethanes, $R_FCH_2CH_2I$, when heated with a large excess of N-methylformamide (NMF) give in high yield, mixtures of predominately $R_FCH_2CH_2OH$, some formate ester and a little $R_FCH=CH_2$. In a study of this process, significant variables were examined, including solvent, reactant ratio, effect of water, and alternative amide reactants. The coproduct from NMF is the amidine salt, $[MeNHCH(=NHMe)]^+I^-$. By contrast, $R_FCH_2CH_2I$ with N,N-dimethylformamide (DMF) and water (one or two mols) gives chiefly the formate ester; the coproduct is $Me_2NH_2^+I^-$. A mechanistic scheme is proposed: in the first step, an alkyl imidate salt, e.g., $[HC(=NH\ Me)OCH_2CH_2R_F]^+I^-$ is formed by O-alkylation of NMF; reaction of the imidate with more NMF gives a tetrahedral intermediate that breaks down rapidly to $R_FCH_2CH_2OH$, and $HC(=NHMe)NMeCHO^+I^-$. The formate ester is derived from the alcohol and this N-formyl acylating agent, in a subsequent step. Analogously, the alkyl imidate salt from DMF and $R_FCH_2CH_2I$ reacts with water as nucleophile (but not with DMF) to give a tetrahedral intermediate that cleaves under stereoelectronic control to formate ester and amine salt, but not to alcohol. Quantitative isolation of amine salt and amidine salt, and observed rates of reaction give solid support to this proposed mechanism.

INTRODUCTION

Among fluorine-containing alcohols, only trifluoroethanol, 2-(F-alkyl)ethanols $[R_FCH_2CH_2OH]$, the so-called 'telomer alcohols' $[H(CF_2CF_2)_nCH_2OH]$, and certain esters of 2-(F-alkyl)ethanols and 3-(F-alkyl)propanols have achieved commercial importance. In the past

0022-1139/86/$3.50

their utilization has been limited by lack of suitable methods of synthesis and high cost. Yet fluorine-containing alcohols and their esters have unique properties, and comprise a versatile class of compounds. In contrast to ordinary alcohols, F-alkyl substituted ethanols are made by special, less well-known methods. The R_F group is derived from tetrafluoroethene (TFE) and from F-alkyl iodides (R_FI), made in two steps from TFE. Reaction of R_FI with ethene [2a,2b] gives 2-(F-alkyl)-1-iodoethane, and under suitable conditions, telomers in high yield. Free radical addition of R_FI to vinyl acetate and subsequent reduction provides $R_FCH_2CH_2OH$ [2a,3]. Though yields are excellent, instability of intermediate $R_FCH_2CHIOAc$ made this process problematical for commercial use [4].

In the meantime other methods have been developed for the synthesis of $R_FCH_2CH_2OH$. Reaction of $R_FCH_2CH_2I$ with oleum forms the sulfate ester; it is readily hydrolyzed [5,6,7]. Similarly, reaction with concentrated nitric acid gives the nitrate ester, which is reduced in a second step to the alcohol [8]. These procedures have been further elaborated. Silver nitrate, or heavy metal ions that form insoluble iodides, are used alone [9] or in conjunction with phase transfer agents, or perfluoroalkanoate ions [10]. The acetate or fumarate esters of $R_FCH_2CH_2OH$ are prepared from $R_FCH_2CH_2I$ and a heavy metal salt such as cadmium acetate [11]; fumarates are also prepared by way of the triethylammonium fumarate salt [12] in an S_N2 type displacement reaction with $R_FCH_2CH_2I$. A serious side-reaction, however, is the formation of the E-2 product, $R_FCH{=}CH_2$. This complication affects the production of the acrylate or methacrylate esters as well, from S_N2 reaction of the corresponding oxyanions, $RCOO^-$. The loss to alkene is minimized by working in an alcohol of low dielectric constant, such as t-pentyl alcohol [13], or in certain solvent mixtures [14]; or by phase transfer-catalyzed reactions with acrylate ion [15] in 2-propanol. Isobutyrate ion in toluene-water mixtures gives a reasonable yield of ester using a phase transfer catalyst [1b].

Oxidative substitution of iodine in $R_FCH_2CH_2I$ has been exploited, a reaction that gives the alcohol under hydrolytic conditions [16]. The intermediate iodoso compound has been implicated in this reaction [17]. A wide range of oxidizing agents is employed and the procedure given by von Werner [18] uses a peroxycarboxylic acid in aqueous acetic acid, with sulfuric acid catalyst at 30°.

A mild, non-hydrolytic method for the synthesis of $R_FCH_2CH_2OH$ from $R_FCH_2CH_2I$ is based on the nucleophilic behavior of amides [19]. Amides can react with an alkyl halide by O-attack to give the imidate salt [20] or by

N-attack to give the N-substituted amide [21]. The imidate salt from reaction of formamide (or N-methylformamide) and dimethyl sulfate is known [22], and amides RC(O)NHR' react with alkyl chloroformates to give the otherwise inaccessible imidates, with loss of CO_2 [23,24]. Though thermally unstable, these imidate salts are hydrolyzed quantitatively to the alkyl ester and amine salt. Even N,N-dimethylformamide (DMF), though not easily alkylated by alkyl chlorides, gives isolable formidates, when BF_4^- or $MeOSO_3^-$ are the counter ions [24].

It is the purpose of this paper to explore the reactions of $R_FCH_2CH_2I$ with amides, and to define more closely the probable mechanism. Reaction of $R_FCH_2CH_2I$ with N-methylformamide (NMF) [25], with DMF and water [26], or with N-methyl-2-pyrrolidinone and water [27] to give $R_FCH_2CH_2OH$ or its formate ester, is described in the patent literature and has been the subject of brief oral reports [28]. However, details relating to mechanism and relationship to extensive previous work [9-24] have not been adequately defined. It is clear from available information, however, that the disclosed method is potentially very useful: it is free from limitations imposed by the use of strong acids, oxidizing agents or basic nucleophiles, may give very high yields of the desired alcohol and ester, and makes use of readily available starting materials. Thus, a more thorough knowledge of the nature and dynamics of this process, and an understanding of its mechanism, are worthwhile goals.

With the mechanism now proposed a seeming contradiction can be explained: why reaction of $R_FCH_2CH_2I$ with anhydrous NMF gives alcohol as major reaction product, whereas, with water present, the product is almost entirely the ester. By postulating the formation of an alkyl imidate intermediate, and by delineating subsequent reactions, it is possible to account for the observed stoichiometry, the rates of reaction, and the differences in reactivity of NMF and DMF.

RESULTS

Reaction of $R_FCH_2CH_2I$ with N-methylformamide

$$\underset{(\underline{1})}{R_FCH_2CH_2I} \quad + \quad \underset{(NMF)}{2\ MeNHCHO} \quad \xrightarrow[140\text{-}150^{\circ}]{} \quad \underset{(\underline{2})}{R_FCH_2CH_2OH} \quad + \quad \underset{(\underline{3})}{R_FCH_2CH_2O_2CH}$$

$$\underset{(\underline{4})}{R_FCH{=}CH_2} \quad + \quad \underset{(\underline{5})}{[MeNH{=}CHNHMe]^+I^-}$$

Simply heating a stirred mixture of $R_FCH_2CH_2I$ (e.g., 1, R_F = C_6F_{13}) with N-methylformamide (NMF) at 140-150° gave alcohol 2 and ester 3 in 95 to 97% combined yield at 98% conversion of 1. About 2 to 4% of alkene 4 was formed. A yield of 98% of 2 and 3 at 81% conversion of 1 has been reported [28b]. The coproduct was not $MeNH_3^+I^-$ as indicated previously [25a], but N,N'-dimethylmethanimidamide hydroiodide 5 (the amidinium salt) [21c]. This fact is significant both for stoichiometry and in deducing the probable mechanism for the reaction. Some results for a few typical preparations, done under different conditions, are given in Table I. GC analysis of anhydrous samples, and response factors obtained from known mixtures, gave the mol amount of each substance. Without adding water, the remaining product mixture was stripped at high vacuum and the crystalline residue (100% yield of 5) was identified by MS, IR, NMR and elemental analysis. Alternatively, water was added and the organic product extracted. NMF was recovered by distillation of the water layer, leaving 5 as residue. Mixtures of 2 and 3 were distilled, and subsequently hydrolyzed in good yield by aqueous base, to pure $C_6F_{13}CH_2CH_2OH$.

Table I

Synthesis of 2-(F-alkyl)ethanols from reaction of 1 with NMF

	1	NMF	Time	Temp	Per Cent Conversion				mol
R_F	mmol	mmol	h	°C	1[a]	2	3	4	2 + 3/4
C_6F_{13}[b]	9.98	147.3	6	140	97.9	65.5	30.2	2.2	43.5
C_6F_{13}[c]	10.0	50.56	10	146	87.6	41.6	28.5	15.0	4.7
C_6F_{13}[d]	94.1	753	11	150	97.9	40.9	52.0	4.9	18.9
F-alkyl[b,e]	103	1000	10	150	99.5	44.8	50.0	3.6	26.3
C_6F_{13}	10.0	147	6	150	99.2	60.3	34.4	4.5	21.0

[a] Per cent of 1 used up; [b] see Experimental for details; [c] a two-phase mixture remained throughout reaction, and became dark in color; impurities were present; [d] after 6 h, amounts present were 54% of 2, 35% of 3, 3.7% of 4 and 6.17% of unreacted 1; two layers separated at 25°; [e] a mixture of 2-(F-alkyl)-1-iodoethanes was used, $R_F = C_6F_{13}$, 46.1%; C_8F_{17}, 30.6%; $C_{10}F_{21}$, 13.7%; $C_{12}F_{25}$, 5.3%; the amounts of products were summed from GC areas, and converted to mols.

The results given in Table I reveal that conversion to 2 and 3 increases with increasing NMF to 1 reactant ratio; thus a large excess of NMF is essential for optimum yield of 2 and 3.

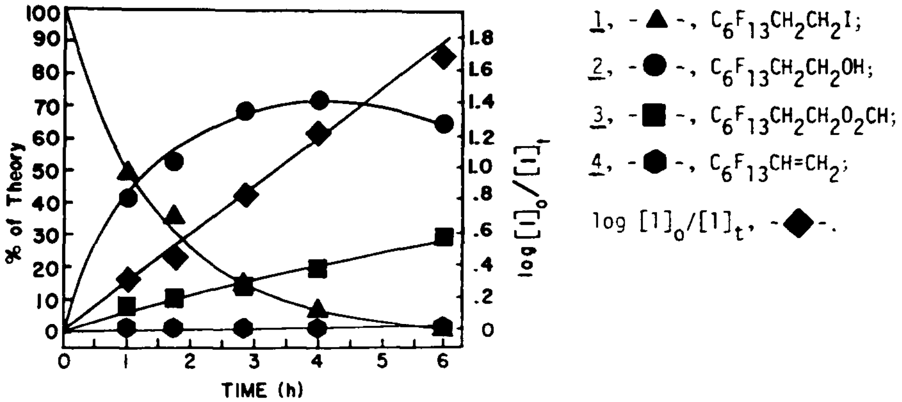


Fig. 1. Reaction of 1 (10 mmol) and NMF (150 mmol) at 140°.

At NMF to 1 mol ratios of less than five to one, immiscible mixtures were formed and resulted in very poor reaction. Reaction temperature is also important: efficiency (mol of 2 + 3/ 4) decreased as temperature was raised from 140° to 150°, while reaction rate increased. At temperatures below 140°, rate of reaction was too slow to be useful, and at 120° only a few per cent conversion occurred in 24 h.

Rate of reaction of 1 and NMF at 140° are plotted in Fig. 1. The concentration of 1 decreased at a first order rate; alcohol 2 and loss of 1 are in nearly a reciprocal relation. Ester 3 was formed by a zero order process, evidently from a growing pool of 2. It is interesting that independent experiments [28b] show that there is no reaction of 2 and 3 under conditions of the process, and that 2 does not react with NMF. Thus, neither are 2 and 3 in equilibrium; nor are 2 and NMF in equilibrium with 3 and methylamine as first proposed [25]. For the formation of 3 from 2, Matsuo, et al. [28b] postulate an unknown intermediate. We now believe that this substance can be identified, and this subject is discussed below.

Reaction of 1 with NMF in NMF/DMF or other liquid mixtures

It was of interest to see whether satisfactory reaction would occur if DMF were used to replace part of the excess NMF needed to maintain miscibility and to provide a polar medium. Results are given in Table II. A clear liquid mixture was formed at 150°, with 25.5 mmol of NMF and 36 mmol of DMF reacting with 10 mmol of 1 (6.15 mol of amides to 1). The conversion of 1 to products was only 33.8%, far less than would have been obtained with 6 mol of NMF alone. In Run #2, 62.1 mmol of NMF and 39.6 mmol of DMF reacted with 10 mmol of 1 (10.2 mol of amides to 1); the

Table II

1 (10 mmol) with NMF (25.5 mmol) and diluent at 150°

Diluent Substance	 mmol	Time h	Per Cent Conversion 1[a]	 2	 3	 4	mol 2 + 3/4
toluene[b]	28	21	32.2	20.1	10.3	1.8	16.9
$t\text{-}C_5H_{11}OH$[c]	27	19	48.1	21.7	20.5	5.9	7.2
DMF	36	6	33.8	24.5	6.6	2.7	11.5
DMF[d]	39.6	6	60.6	47.8	9.0	3.8	14.9

[a] Per cent of 1 used up; [b] two phases appeared after 3 h; [c] two phases appeared after 15 h; [d] used 62.1 mmol of NMF; compare with Run # 2 of Table I.

conversion to products was 60.6%, again far smaller than the 93.2% reaction in Run #3 of Table I. In both reactions, with DMF, a clear homogeneous liquid mixture was present throughout. And in both cases efficiency was smaller than for NMF alone. Using a 10:1 mol ratio of NMF to 1, 95% yield of 2 and 3, and 5% of 4 is obtained in 6 h at 145° [28b]. Accordingly, DMF cannot substitute for NMF in the reaction with 1.

This conclusion is made stronger by results of reactions in which toluene or t-amyl alcohol were used. Though reaction was slower in toluene (32.2% in 21 h at 150°), than in NMF/DMF mixtures, better efficiency was achieved. The alcohol solvent gave faster reaction than in toluene, perhaps a reflection of the greater polarity of the alcohol, but side reaction to alkene 4 was greater. However, both solvents show that even at a reactant ratio as low as 2.55 mol NMF to 1, conversion to products can be achieved. The reaction of 1 and amides has been studied in 1,4-dioxane and in acetonitrile and the results are complementary to those given here [25].

Reaction of 1 with DMF and water

Conversion of 1 to mixtures of 2, 3 and 4 by heating 1 with DMF and water is known [26]. Matthews *et al.* [29] found that DMF with 1-bromooctane requires two mol of water for complete conversion to 1-octanol (the second mol to hydrolyze the ester); the salt coproduct is $Me_2NH_2^+Br^-$. However, Hayashi *et al.* [26] found that with 1, a large excess of DMF is required to give optimum yield of 2 and 3, with a minimum of 4. Mol ratios of 15:1 or higher of DMF to water give selectivity (per cent conversion) of more than 90% to 2 and 3 [26a]. Table III lists both old and some new results.

Table III

1 (10 mmol) with DMF and water at 150°, 6 h

DMF	Water	Per Cent Conversion			mol
mmol	mmol	2	3	4	2 + 3/4
300[a]	15	16.5	80.6	2.9	23.5
300[b]	24	32.0	63.6	4.4	21.7
300	23	29.7	63.6	6.7	13.9
220[a]	12	4.8	91.5	3.7	26.0
220[a]	60	55.6	23.8	20.6	3.8
220[c]	66	77.1	14.6	8.1	11.2

[a] Reported by Hayashi and Matsuo, Ref. 26a;

[b] reaction done at 142° (inside temperature); see Table VI, Experimental;

[c] trifluoroacetic acid (2.85 g, 25 mmol) was added, reaction for 6.5 h; cf. ref. 26b.

In a seeming contradiction, reaction of 1 with DMF and water gives predominately ester, which is subsequently hydrolyzed to alcohol. This is seen in the increased amounts of 2 found as the water concentration is increased. This fact is also apparent from the rates of reaction and product formation shown in Figure 2. Consistent with previous work [26], the concentration of 1 decreased by first order kinetics. The change in concentration of 2 and 3 varied in a complex manner. The rate of formation of 4 was very small and therefore is not given. The final amount of 4 was 4.4% of theory, and in the GC samples was too small to be quantified. However, as is clear from the results of Table III, increasing the water concentration to 60 mmol (Run #5) greatly increased the conversion to 4,

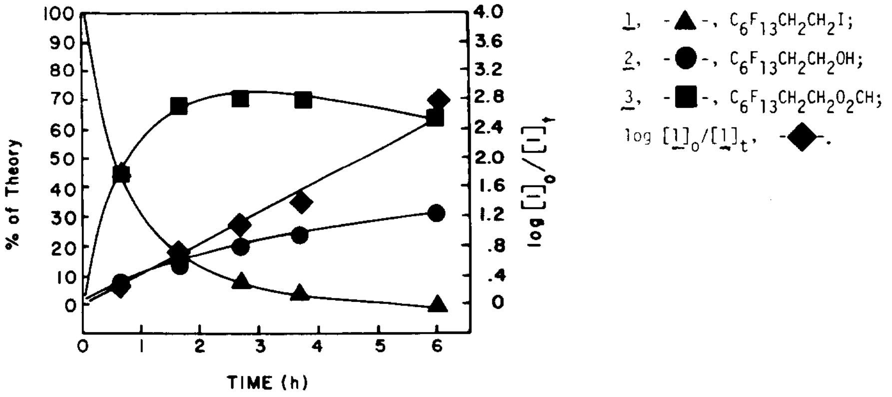


Fig. 2. Reaction of 1 (10 mmol), DMF (301 mmol) and water (24.2 mmol) at 142

and thus cannot be used to increase the rate of hydrolysis of 3 without loss of the desired product. To some extent an acid catalyst (Run #6) ameliorated this situation. It was previously demonstrated that in this system, no reaction occurs without water [26, 29]. The rate constant for reaction of 1 with DMF and water is slightly greater, than for NMF and 1 without water.

Reaction of 1 with N-2-Propenylformamide and other alternative amides

N-2-Propenylformamide (NPF) was heated with 1 at 143° to 150°, both with water as coreactant as for DMF, and without water present as for NMF. Mixtures of 2, 3, 4 and N,N'-bis-(2-propenyl)methanimidamide salt (6) were produced at very high efficiency, as given in Table IV. Decreasing the mol ratio of NPF to 1 and increasing the temperature increased the loss to 4, as for reactions using NMF. Water as coreactant speeded up the reaction of

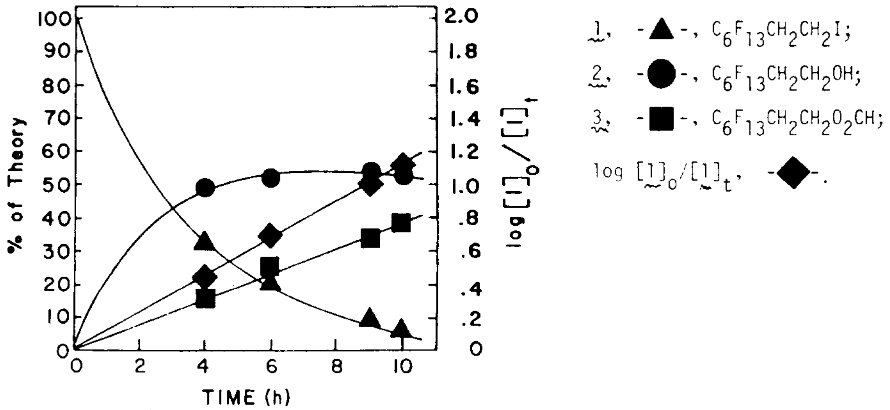


Fig. 3. Reaction of 1 (10 mmol) and NPF (150 mmol) at 140°.

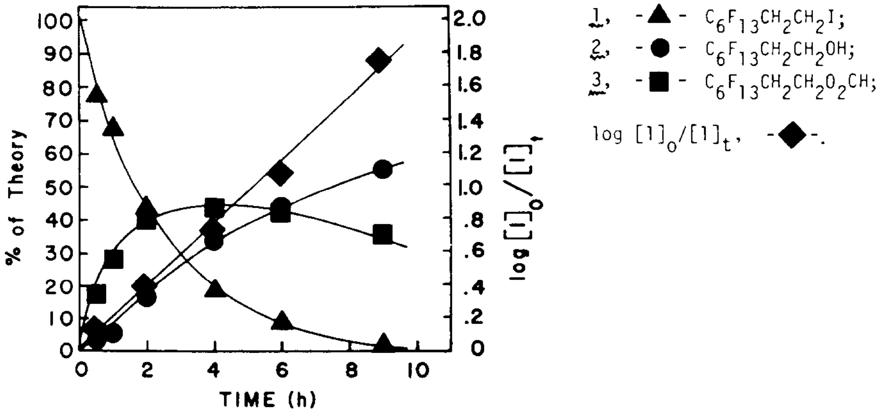


Fig. 4. Reaction of 1 (10 mmol), NPF (150 mmol) and water (22 mmol) at 141°.

1, and increased the rate of ester formation. This result confirms the observation of a similar effect in reaction of 1 with DMF. However, it is also clear from a comparison of Figure 3 (no water) and Figure 4 (22 mmol of water, Run #3, Table IV), a reaction similar to that of NMF with 1 occurred in the anhydrous system. By contrast, with water present, a complex sequence of reactions has ensued, and alcohol 2 and ester 3 were produced by competing processes. It is most significant that rate of formation of ester greatly exceeded that of alcohol, with water present as a nucleophile. This is a clear indication of the relative reactivity of an amide such as NMF or NPF, and of water, in bringing about product formation from the intermediate alkyl imidate.

Table IV
Reaction of 1 (10 mmol) with N-(2-propenyl)formamide

$$\underset{(1)}{C_6F_{13}CH_2CH_2I} + NPF \longrightarrow \underset{(2)}{C_6F_{13}CH_2CH_2OH} + \underset{(3)}{C_6F_{13}CH_2CH_2O_2CH} + 4 + 6$$

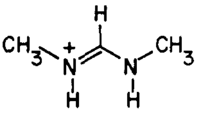
NPF mmol	Time h	Temp °C	Per Cent Conversion 1^b	2	3	4	mol $2 + 3/4$	k^a
150	6	150	68.7	46.5	20.6	1.55		
	13.2		99.1	46.0	49.1	4.0	23.8	--
100^c	6	150	69.0	45.3	17.4	2.5		
	11		81.2	48.4	28.1	3.0		
	18		90.9	42.9	43.5	4.0	21.6	1.8
150^d	4.0	141	81.3	33.5	43.5	4.3		
	9.0		99.2	55.4	35.6	7.2	12.6	5.2
150	4.0	140	66.5	49.6	16.0	0.87		
	6.0		79.4	52.4	25.6	1.4		
	9.0		91.9	54.4	34.0	2.5		
	10.0		93.6	54.4	38.6	2.4	43.5	3.2

[a] Slope of straight line log $[1]_o/[1]_t$ vs. time, $k = n \times 10^{-5}\ sec^{-1}$; [b] Percent of 1 used up; [c] clear reaction mixture; [d] contained 22 mmol of water; in a sealed tube the mixture became clear in 2 h; see Table VI, Experimental.

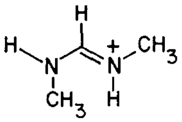
1,2-Ethanyl-bis-formamide ($HCONHCH_2CH_2NHCHO$, EBF) possesses two amide functions in one molecule. Thus, it potentially should reduce by half the mol ratio required for reaction with 1. Unfortunately, at a 5 to 1 mol ratio of EBF to 1, an immiscible mixture formed at 150°, which gave only about 10% reaction in 22.5 h. DMF was added to facilitate mixing of the two phases. When a total amount of DMF and EBF equalled a 24 to one mol ratio of amides to 1, the reaction was driven to completion in 24 h. The conversion to products (as determined by GC) was: 2, 31.4%; 3, 51.0%; and 4, 16.7%. The aqueous layer in the work-up was extracted with dichloromethane and the mixture of 2 and 3 was distilled; the yield was 80% of theory. The high conversion to 4, however, renders this an unsatisfactory system for the synthesis of 2. Several other potentially useful amides were investigated and the results will be reported later.

Isolation and properties of N,N-dialkylmethanimidamide salts

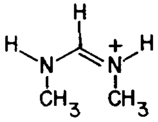
Salts of 5 are known [30,31]. The picrate was used to identify 5 [22c], and others have been studied extensively in solution [31a-c] and as metal complexes [31d-e]. The NMR spectrum of 5 at ambient temperature up to 120° gave signals for two non-equivalent methyl groups at $\delta 2.78$ and $\delta 3.04$ (1 to 1 intensity). The ratio of methyl to vinyl protons was six to one. This result is consistent only with 5b as the major contributing form. Above 120° the signals coalesced as for DMF. Mass spectrum analysis gave further support for structure 5. Major fragments observed were m/e = 42 (base peak), $CH_3N{\equiv}CH$; and mol ion, m/e = 72, $[CH_3N{=}CHNHCH_3]^+$. The N,N'-bis(2-propenyl)methanimidamide salt $[HC({=}NHR)NHR]^+I^-$ (6), R = $CH_2{=}CHCH_2{-}$, was similarly identified. It gave an NMR with two non-equivalent CH_2 groups, analogous to 5b.



5a



5b

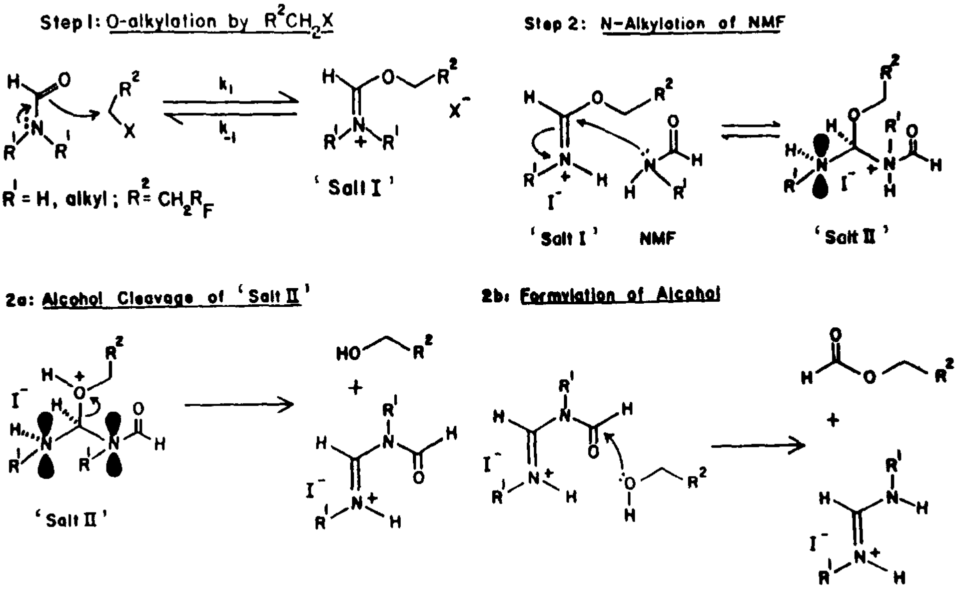


5c

DISCUSSION

The key intermediate in these reaction systems is the imidate salt ('Salt I', Scheme I), derived from NMF, DMF or NPF and 1. Analogous compounds have been obtained in pure form [20,21]. For example, methyl sulfate and NMF gives crystalline salt $[HC({=}NHMe)OMe]^+ MeSO_4^-$, at room temperature [22c]. Heating this salt with more NMF gives $\overset{+}{\text{MeNHCH=NHMe}}\text{MeSO}_4^-$ (analogous to 5) and methyl formate [22c]. NMF and many other mono-substituted amides react with ethyl chloroformate to give the imidate hydrochlorides; e.g., $\text{HC(OEt)=NHMe}^+\text{Cl}^-$ [23, 24]. Reaction of 1 with NMF apparently occurs only above 120° at an appreciable rate, and at this temperature the imidate salt ('Salt I') reacts further with another molecule of NMF. 'Salt I' from 1, therefore, has not been isolated.

According to Scheme I, the imidate ester forms reversibly in the first step of a sequence of reactions; hence, the observed first order kinetics for the disappearance of 1, when using a large excess of amide (rate = k [1][amide]^0). In subsequent steps, 'Salt I' converts to alcohol 2 by displacement with NMF. A tetrahedral intermediate ('Salt II') is formed by 'N-attack' of NMF (step 2), and then breaks down to alcohol and an N-formylamidine salt (step 2a). This accounts for the rapid and preferential formation of alcohol (Figs. 1 and 3), which is made more



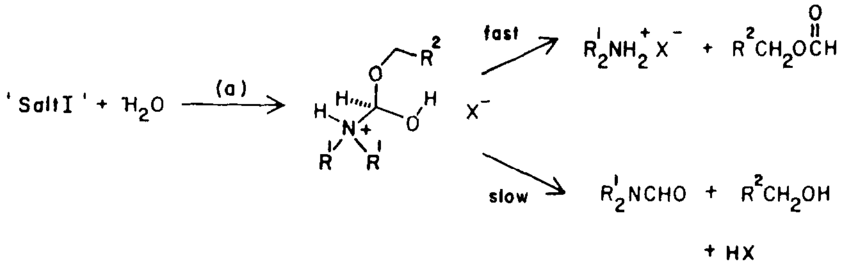
Scheme 1. Alcohol Formation and esterification from reaction of ambidentate N-methylformamide with R^2CH_2X.

probable by resonance stabilization of the amidine salt. Slower reaction of the alcohol with the N-formylamidine salt provides the formate ester (step 2b). This acylation is like that of an anhydride with an alcohol; and the coproduct is the N,N'-dialkylmethanimidamide salt 5 or 6. Thus, the previously obscure reaction sequence: 1 ——> 2 ——> 3 + 5 (or 6), can be given a rational explanation in steps 1 to 2b of Scheme I. The small amount of alkene 4 obtained in these reactions could be caused by acid-catalyzed dehydration of 2. This reaction is promoted by increasing acidity, by higher temperature and by higher concentration (Tables I, III and IV). Any remaining N-formylamidine salt would be hydrolyzed during aqueous work-up to amidine salt 5; so far, attempts to detect any of the intermediate salts from 1 have not succeeded.

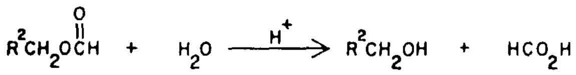
Reaction mechanism for reaction of 1 with DMF and water

As an imidate, 'Salt I' is very susceptible to attack by nucleophiles, even by the ambidentate amide NMF, but not by DMF [20,21b]. The imidate ester salt $[HC(=NMe_2)OCH_2CH_2C_6F_{13}]^+I^-$ (7) from DMF and 1, however, does react with water, an amine such as ammonia or with H_2S [20,

Steps 3a to c: Water Displacement on 'Salt I'



Step 4: Hydrolysis of Ester



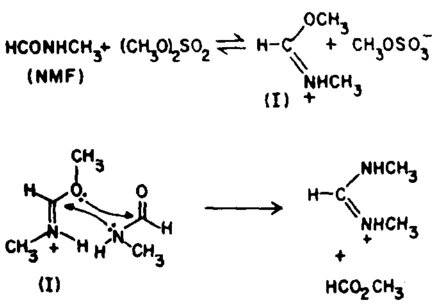
$$R^2CH_2O\overset{O}{\overset{\|}{C}}H + H_2O \xrightarrow{H^+} R^2CH_2OH + HCO_2H$$

Scheme 2. Water addition to imidate ester, with amine salt and ester cleavage; hydrolysis of ester to alcohol and formic acid.

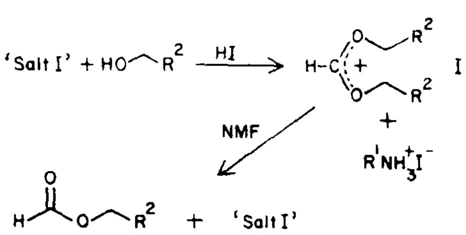
21b]. In the system at hand, water reacts with 7 to give predominately ester 3, and a little alcohol (Fig. 2). Optimum conditions (large excess of DMF, one mol of water) give ester because the imidate 7, though slowly and reversibly formed, can readily react with a small nucleophile such as water. First order kinetics are still obeyed and imidate salt formation is rate controlling. Steps 2, 2a and 2b, however, are not observed with DMF as nucleophile. Perhaps steric hindrance prevents N-attack by DMF on 'Salt I'; the congestion caused by three or four methyl groups in the intermediate complex of step 2 must be considerable. The imidate $[HC(=NMe_2)OMe]^+ MeSO_4^-$ decomposes to starting materials when heated with DMF [22d].

Steps for reaction of imidate from 1 and DMF ('Salt I', R^1, R^1 = Me) with water are shown in Scheme 2. The tetrahedral intermediate breaks down rapidly to the amine salt and formate ester 3 [20,32]. Hydrolysis of 3 to alcohol 2, occurs in a subsequent step with excess water. Preferential cleavage to ester and amine salt is favored by non-bonded electron pair interactions and the stability of the amine salt. This conclusion is given convincing support by the work of Schmir and coworkers [32] and by Deslongchamps [33]. Thus, imidates 8 and 9 give ester and amine salt exclusively at a pH below 8.5: $[RC(=NMe_2)OEt]^+$; 8, R = Me; 9, R = C_6H_{11}. Hydrolysis to alcohol and amine occurs only at higher pH [33]. This behavior has been cited even in recent work in related systems [34].

As given in Table III, hydrolysis of ester 3 to alcohol 2 does occur when an excess of water is used, and is catalyzed by acid, such as trifluoroacetic acid. As might be expected, however, alkene 4 is then increased in yield, by higher acidity and greater polarity of the medium.



Scheme 3. Formate ester from N-methylmethanimidate salt by concerted reaction.



Scheme 4. Alcoholysis of imidate; amine salt formation; NMF displacement of formate ester.

In reactions of 1 with NMF/DMF mixtures without water present as nucleophile, DMF cannot complete the sequence of steps 1 to 2b. Reaction rate is slowed down, which implies that the reverse of step 1 has a considerable rate, and also that imidate ester from DMF does not go on to form product. In this sense, DMF is not just a solvent for NMF. Only as the imidate from DMF reverts to DMF and 1, can 1 react with NMF.

An alternative mechanism, suggested earlier by Bredereck et al. [22c] for reaction of 'Salt I' with NMF would also account for ester being formed (Scheme 3). However, the observed initial predominant formation of alcohol argues against ester as the primary product of imidate salt displacement. Kantlehner [20] considered that alcoholysis of 'Salt I' gives an ortho ester and $R'NH_3^+I^-$ (amine salt); subsequent reaction with NMF gives formate ester (Scheme 4). This mechanism, however, does not accord with experimental results either. Amidine salt 5 is the observed coproduct, and only traces of amine salt are formed.

EXPERIMENTAL

Materials and physical methods

NMF (contained 0.25% water), DMF (contained 0.65% water), and 2-propenamine were obtained from Aldrich Chemical Co. 2-(F-Hexyl)-1-iodoethane (1) and 2-(F-alkyl)-1-iodoethane mixture were obtained from the E.I. du Pont de Nemours and Co. IR spectra were taken using a Perkin Elmer grating Infrared spectrometer 337 or 1430. NMR spectra were obtained using a Varian T-60, or HA-100 spectrometers, with the assistance of Dr. R. Rodebaugh. Mr. Ken Ng carried out mass spectrum analyses. TLC, combustion analysis and Karl Fischer analysis were performed by the Analytical Division at Ciba-Geigy Corp., Ardsley, N.Y.

GC Analysis was done using either a Sargent-Welch or a similar Gow-Mac thermoconductivity apparatus. The instrument was fitted with an 8-ft by 1/4 inch column, packed with 10% of QF-1 fluorosilicone oil on acid-washed, base-washed, silanized Chromosorb W (60-80 mesh) packing. The instrument was programmed to go from $80^{o}$to 180^{o}, at a rate of 10^{o}/min. Helium flow was 30 mL/min. Other columns of several types and other conditions were not satisfactory for the separation of the compounds of this study. A standard mixture was prepared to determine response factors as follows: 4, retention time 4.1 min, 4.10% area, 0.4305 response factor; toluene, 6.4 min, 50.98%, 1.000 response factor; 2, 10.3 min, 13.62% area, 0.4794; 1, 11.2 min, 6.64% area, 0.3832; 3, 12.3 min, 24.65% area, 0.4313 (average of four analyses, variation 0.1%).

Standard reaction procedures

(a) Method A

A glass ampoule (tissue culture tube, 20 by 125 mm) sealed by a tightly-fitted Teflon-lined screw cap, was charged with reactants, immersed in a constant temperature bath, and stirred by a magnet bar. In certain cases a larger, heavy-wall pressure tube (Fischer-Porter) was used. No loss in weight occurred during reaction. The reaction products were drowned in water, extracted with dichloromethane, dried and partially evaporated off. A GC sample was removed, an internal reference weighed in and the amounts of the substances that were present determined by replicate runs, and calculated using response factors. The organic products were distilled and analyzed as required. The aqueous layer was also distilled under reduced pressure to recover the excess amide, and the residue pumped off under high vacuum to obtain the salt product. Hygroscopic halide salts were dried in vacuo over P_2O_5, and stored in a desiccator for analysis.

(b) Method B

A 50 mL flask was fitted with a 'Y-tube' and a condenser that was attached to a -78^o cold trap and bubbler tube (to indicate gas evolution) and was stirred by magnet bar. The flask was immersed in a constant temperature bath, and at intervals of time was briefly cooled, while a sample was withdrawn by capillary pipet through the cooled condenser. GC analysis was run on the anhydrous mixture to prevent hydrolysis of salts.

(c) Method C

A reactor tube, constructed with a sampling port on the side to facilitate removal of samples without disturbing the reaction system, was immersed in a constant temperature bath, purged with nitrogen through a sintered disc inlet tube, and vented through a -78^o trap as above. Samples were removed and processed as for Methods A and B.

N-(2-Propenyl)formamide (NPF)

2-Propenamine (57.1 g, 1.00 mol) was cooled to 12^o (ice-water bath) and while stirring, methyl formate (120.1 g, 2.00 mol) was added slowly during 30 min at 12-14^{o} (bath temperature). Refluxing occurred briefly. Then heating was continued for 14 h and volatile material (82 g) was removed slowly through a 10-inch Vigreaux column, fitted with a total reflux, partial take-off head, up to bp 60^{o} (pot temperature 123^{o}, bath temperature, 130^{o}). The residual oil (89.8 g) was fractionated using an 8-inch Podbielniak packed column; forerun, bp 98-100^{o}/10 mm, n_D^{25} 1.4587, 1.57 g; and N-2-propenylformamide (NPF), bp 100^{o}/10 mm, n_D^{25} 1.4640; n_D^{25} 1.4622, 75.29 g, 90.3% yield; hold-up, 5.33 g. IR: 3300, 3050 (NH), 2995 (CH=), 1690 to 1650 (C=O and C=C), 1525 (CONH), 1425, 1390 and 1240 (CH deformation), and bands at 1150, 1090, 990, 965 and 910 cm^{-1}. NMR ($CDCl_3$, 100 MHz,δ): 3.86, t, 2 protons, CH_2N; 5.20, m, 2 protons, CH_2=; 5.80, m, 1 proton, =CH; 7.07, broad, exchangable, NH; 8.14, s, 1 proton, CHO. Analysis: Found: C, 56.7; H, 8.4; N, 16.4. C_4H_7NO requires C, 56.5; H, 8.3; N, 16.5.

1,2-Ethanyl-bis-Formamide

This substance was prepared in quantitative yield by the method of Vail *et al.*[35] mp 106-109^{o}. NMR (100 MHz,δ): 2.99, m, four protons, coupled to NH, and affected by rotational restrictions, CH_2; 7.73, broad, exchangeable, two protons, NH; 7.83, s, two protons, CHO.

Reaction of 1-Iodo-2-(F-hexyl)ethane (1) with NMF

(a) Mol ratio of one to five (1 : NMF)

1, (4.7616 g, 10.04 mmol) and NMF (2.9864 g, 50.56 mmol, dried over Molecular Sieves) were reacted by Method A, at 146^{o}. A dark orange layer formed over a colorless lower layer. The mixture was cooled, poured into water (10 mL) and the heavy oil (3.7500 g) was washed again with water (1 mL) and dried (Molecular Sieves). GC gave: 4, 15.0% of theory; 2, 41.9%; 1, 12.4%; and 3, 28.5%. Impurities of longer retention times were observed, total 1.29%.

(b) Mol ratio of one to 14.7 (1 : NMF)

1 (4.82 g, 9.98 mmol, 98.2% pure) and NMF (8.70 g, 147 mmol) were reacted by Method B, at 140^{o}. There was no sign of gas evolution during heating; thermal decomposition of NMF was not observed. Molar amounts of each substance present in the samples taken are listed in Table V, and calculated as per cent of theory; results are also plotted as Figure 1.

Table V

Reaction of 1 and NMF at 140°; mol ratio of 1 to NMF = 1 to 14.7

Time, min	60	105	170	240	360
Substance	Per cent of theory				
1	49.1	35.7	15.1	6.88	2.11
2	41.6	52.2	69.5	72.1	65.5
3	8.25	10.9	14.1	19.7	30.2
4	1.0	1.23	1.3	1.3	2.19
$\log[\underline{1}]_o/[\underline{1}]_t$	0.303	0.456	0.839	1.229	1.70
k[a]	5.05	4.34	4.94	5.12	4.72

[a] first order rate constant, all values x 10^{-3} min^{-1}; avg = 8.05 x 10^{-5} sec^{-1}.

A portion (11.28 g, 83.43%) of the remaining product mixture was distilled under reduced pressure, using a Dry Ice cooled trap, to give volatile products, bp 43°/0.75 mm to 28°/0.12 mm, 8.66 g; and trap liquid, 0.88 g. The bath was heated to 60°. White, crystalline, very hygroscopic N,N'-dimethylmethanimidamide hydroiodide (5), 1.54 g, remained as residue (92.5% of theory). The total recovery of volatile products by GC was also 92.5% of theory.

(c) Isolation of 2, 3, and Salt 5; recovery of NMF

1 (45.49 g, 94.13 mmol) and NMF (44.5 g, 753 mmol) were charged to a 100 mL, flat-bottomed Fischer-Porter glass reactor vessel, cooled to 0°, and evacuated and filled with nitrogen three times. The mixture was heated to 150°, while stirring by magnet bar, and became homogeneous after 2.5 h. It was sampled at 6 h and 11 h. Water (100 mL, twice) was added first to the lower layer, and then to the upper layer. The aqueous layer was extracted with dichloromethane (twice, 25 mL) and dried. Volatile substances were removed by heating to 70°/10 mm (10-inch Vigreaux column); the residue (32.78 g) contained (by GC) 1.85% of 1, 0.52% of 4, 40.5% of 2 and 56.25% of 3. (See below for hydrolysis.) The aqueous layer was stripped on a rotary evaporator to 70°/15 mm, then distilled. This gave a forerun, bp 23-68°/10 mm, 0.80 g; and pure NMF, bp 83°/10 mm, n_D^{25} 1.4312, 30.1 g. The residue, heated to 168°, gave crystalline 5, 17.5 g (93.0% of theory for complete reaction). The recovery of NMF was 87.9% of theory. The salt residue was dried over phosphoric anhydride *in vacuo*. The

water-soluble, very hygroscopic solid 5 HI (nc) gave IR (Nujol mull): very strong bands of NH at 3500-3200 [21e]; very strong C=N band at 1880-1700; NH bending at 1550; and bands at 1450, 1380, and 1350 cm^{-1} not in NMF; bands at 1180, 1125, 1010 (very strong) and at 950 cm^{-1}. NMR (100 MHz, DMSO-d^6, run at 80° and 120°, δ): 2.78 and 3.04, 1:1 intensity (10 Hz separation) of two non-equivalent methyl groups; and 8.00, s, one proton of CH=N; the area ratio of methyl to CH= was 6:1. On heating to 120°, the two signals at 2.78 and 3.04 coalesced [31a]. Mass spectrum of the salt gave a fragmentation pattern having a base peak with m/e = 42 $(CH_3N{\equiv}CH)^+$; at m/e = 72 for the molecular ion, $(CH_3N{=}CHNHCH_3)^+$; and peaks at m/e = 31 (CH_3NH_2), and at m/e = 127 and 128 (I and HI, resp). About 3 to 4% of $CH_3NH_3^+I^-$ appeared to be present. Analysis: Found: C, 17.8; H, 4.21; N, 13.6; I, 62.0. $C_3H_9N_2I$ requires C, 18.0; H 4.54; N, 14.0; I, 63.3.

2-(F-Alkyl)ethanols

(a) 2-(F-hexyl)-1-ethanol

A 2-(F-Ethyl)ethanol/formate (2,3) mixture (32.78 g, 83.5 mmol) and sodium hydroxide (3.20 g, 80.0 mmol) in water (35 mL), was stirred for 7 h at 85°; a sample showed unhydrolyzed 3. After additional heating for 15 h at 62°, the product (28.96 g) was dried and distilled in vacuo to give 2, bp $70-71^{\circ}/10$ mm, 26.44 g (87% of theory, GC, 97-99% pure); and a fraction bp $71^{\circ}/10$ mm, n_D^{25} 1.3157 (100% pure 2).

(b) Homologous (2-F-alkyl)-1-ethanols

Similarly, the 2-(F-alkyl)ethanol/formate mixture from above (47.45 g, ca 51.1 mmol of 2-(F-alkyl)ethanols and 53.1 mmol of 2-(F-alkyl)ethyl formates, by GC) was stirred with potassium hydroxide (5.6 g, 100 mmol) disdissolved in water (50 mL) at 83°, under a total reflux head set at high reflux ratio. Distillation product (1.47 g) was collected during 20 h. GC of the separated oil layer (40.03 g; unchanged after 20 or 43 h) gave: 2-(F-alkyl)ethenes, 1.40 g, 3.34% of theory; 2-(F-alkyl)ethanols, 36.45 g, 92.3%; 2-(F-alkyl)-1-iodoethanes, 0.42 g, 0.77%; and 2-(F-alkyl)ethyl formates, 1.63 g, 3.49%.

2-(F-Hexyl)ethyl formate (3)

2-(F-Hexyl)ethanol (2, 11.43 g, 31.41 mmol), formic acid (15.6 g, 340 mmol, 90%) and toluene (25 mL) was heated while stirring under a

Dean-Stark trap at 88-100° for 8 h; GC showed 6.5% of 2. Formic acid (5 mL, 7.8 g, 170 mmol) was added and heating continued for 6 h at 75-112°. Distillation (8-inch Vigreaux column) gave forerun, 0.55 g, and 3, bp 78°/18 mm, n_D^{25} 1.3196, 8.29 g (GC: 4.31% of 2, 0.78% of 1, and 97.5% of 3). Hold-up and residue was 0.76 g. Conversion to 3 was 71.8% of theory. NMR ($CDCl_3$, 100 MHz, δ): 2.5, 2 protons, multiplet, R_FCH_2; 4.0, t, J = 8 Hz, CH_2OH (4.5% relative area); 4.5, 2 protons, t, J = 8 Hz, CH_2O_2CH; and 8.0, 1 proton, s, CHO. Analysis: Found: C, 28.3; H, 1.46; F, 63.1. $C_9H_5F_{13}O_2$ requires C, 27.6; H, 1.28; F, 63.0.

Reaction of 1 with DMF and water at 142°

1 (4.890 g, 10.12 mmol, 98.1% pure), DMF (21.99 g, 300.9 mmol, contained 8.2 mmol of water) and water (0.2894 g, 16.06 mmol, total 24.2 mmol) was heated at 142° by Method C (inside temperature was 142°, bath temperature was 146°). Samples were removed for GC analysis. See Table VI below and Figure 2. After 6 h the remaining reaction mixture was added to water (50 mL) and the oil extracted again with water (20 mL). The aqueous layer was extracted in turn with dichloromethane (10 mL and 20 mL) and dried ($MgSO_4$). Solvent was removed, and an aliquot sample gave substances as follows: 1, 0.2% of original material, 2, 31.43% yield, 3, 64.0% yield and 4, 0.45% yield. The aqueous layer was stripped on a

Table VI

Reaction of 1 with DMF and water at 142°; GC Analyses

Time, min	40	100	160	220	360
Substance	mmol	mmol	mmol	mmol	mmol
1	4.65	1.99	0.814	0.434	0.033[a]
2	0.938	1.51	2.05	2.46	3.01[a,b]
3	4.41	7.62	7.36	7.25	6.49[a,b]
4	---[c]	---[c]	---[c]	---[c]	0.47[a]
$\log[1]_0/[1]_t$	0.338	0.706	1.09	1.37	2.49
k (x 10^{-5} sec^{-1})	14.1	11.8	11.4	10.4	11.5

[a] from total product mixture sample, obtained by extraction;

[b] from probe sample the amount of 2 was 3.34 mmol and of 3, 6.73;

[c] the amount was too small to quantify in the probe sample.

rotary evaporator to remove both DMF and water; and the residue pumped down to 1.5 mm of mercury at 100° for 2 h. The crystalline solid (1.45 g, 90.8% of theory for N,N-dimethylammonium iodide) gave a single spot in TLC analysis, and an IR, having bands at 2400, 1575, and at 1010, 875, and 850 cm^{-1} identical with a published spectrum [36].

Reaction of 1 with N-(2-propenyl)formamide (NPF)

(a) At 150°

1 (4.85 g, 10.0 mmol) and NPF (12.77 g, 150 mmol) was heated in a bath at 151° using Method A. A clear yellow liquid mixture was formed. The tube was cooled and a sample removed for GC. The remaining material was transferred to a 50 mL flask and heating continued by Method B. The inside temperature was 150° and the outside temperature was 153°. There was no gas evolution during heating. After 13.2 h of reaction, sample two was taken and analyzed by GC. Results are listed in Table IV.

(b) At 140°; Isolation of N,N'-bis(2-propenyl)methanimidamide hydroiodide (6)

1 (4.85 g, 10.0 mmol) and NPF (12.77 g, 150 mmol) stirred at 140° (bath at 143°) became homogeneous in 30 min. Reaction reached 94% conversion of 1 in 10 h. (See Table IV and Figure 3). The reaction mixture was was worked up as for NMF reaction above. NPF was recovered, bp 44°/ 0.18 mm, 9.14 g, 91.0% of theory. The hygroscopic salt residue (2.58 g) was 103% of theory for N,N'-bis(2-propenyl)methanimidamide hydroiodide (6, nc). TLC on silica gel ($CHCl_3$/MeOH/NH_4OH/H_2O) showed non-identity with CH_2=CH-$CH_2NH_3^+I^-$ and NPF (present in trace amounts, with two other minor impurities. IR (smear on KBr) gave strong band (NH) at 3200; νCH=N and νCH=CH at 1690 to 1650; NH^+, 1540; and bands at 1430, 1426, 1380, 1330, 1240, 1145 cm^{-1}; also CH_2=CH at 990 and 930 cm^{-1} (very strong). NMR (DMSO-d^6, run at 80 and 120°, δ): 4.00, two non-equivalent, staggered doublets, 4 protons, CH_2 and CH_2' groups; 5.13, complex, 4 protons, two CH_2= groups; 5.69, complex, 2 protons, two =CH groups; 8.13, 1 proton, CH=N; 8.88, broad, exchangeable, two protons, 2 NH groups. Analysis: Found: C, 31.0; H, 5.1; N, 10.5; I, 50.9 (total); 51.7 (ionic). $C_7H_{12}N_2I$ requires C, 33.3; H, 5.2; N, 11.1; I, 50.3.

Table VII

Reaction of 1 with NPF and water at 141°

Time, h	0.5	1.0	2.0	4.0	6.0	9.0
Substance	Per Cent of Theory					
1[a]	78.4	67.3	43.0	18.7	8.1	1.8
2	3.90	4.59	16.0	33.5	43.7	55.4
3	17.4	28.1	40.1	43.5	41.9	35.6
4	---[b]	---[b]	---[b]	4.3	6.3	7.2
$\log[1]_0/[1]_t$	0.0942	0.181	0.380	0.697	1.1	1.8
k $(\times 10^{-5} sec^{-1})$	5.23	5.04	5.28	4.88	5.1	5.4

[a] Per cent of 1 remaining; [b] amount too small to quantify.

Reaction of 1 and NPF with water at 141°

1 (2.3818 g, 4.928 mmol), NPF (6.3870 g, 75.05 mmol) and water (0.20 g, 11 mmol) was heated by Method A at 141° (bath at 144°). Samples taken for GC are listed in Table VII, plotted in Figure 4, and summarized in Table IV.

Reaction of 1 with 1,2-Ethanyl-bis-formamide (EBF) at 150°

1 (23.27 g, 48.20 mmol) and EBF (28.02 g, 241.3 mmol), when heated at 150° for 22.5 h gave two immiscible layers (Method B). GC gave 1, 90.9% (area); 2, 4.7%; 3, 2.6%; and 4, 1.5%. DMF ((5.00 g, 68.4 mmol, 5.07 mL) was added and heating continued for 6 h, but the mixture remained immiscible. GC gave 1, 66.3% (area); 2, 20.4%; 3, 8.5%; and 4, 4.8%. Again, DMF (9.82 g, 135 mmol, 10.4 mL) was added and the mixture was heated at 150° for 17.5 h. The immiscible mixture was cooled. Water (100 mL) was added, and the organic layer (17.70 g) gave, by GC (with toluene reference), 1, 0.87% of theory; 2, 31.4%; 3, 51.0%; and 4, 16.7%. To recover remaining product, the aqueous layer was extracted (dichloromethane, 10 mL) and combined material distilled (16-inch spinning band column). A forerun, 2, 3 and DMF, bp 56-62°/11 mm, n_D^{25} 1.3470, 3.19 g; a mixture of 2 and 3, bp 62-63°/11 mm, n_D^{25} 1.3195, 11.04 g; and a solid residue, 1.30 g, were obtained. IR, νOH, 3450 cm^{-1} and νC=O, 1735 cm^{-1}.

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