

Organic Reactions in Liquid Hydrogen Fluoride. II. Synthesis of Imidoyl Fluorides and N,N'-Dialkyl-2-alkylaminomalonamides^{1,2}

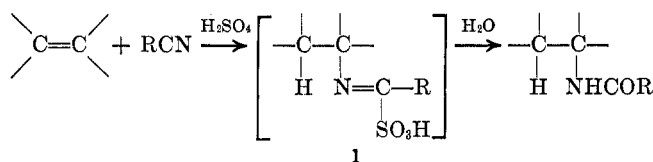
JOHN R. NORELL

Phillips Research Center, Phillips Petroleum Company, Bartlesville, Oklahoma 74003

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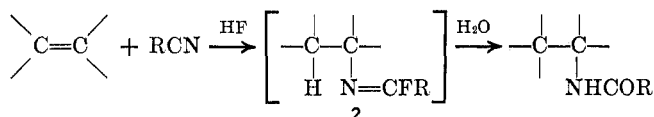
Imidoyl fluorides (RN=CFR') have been isolated for the first time as intermediates in the condensation of olefins with nitriles (Ritter reaction) using liquid hydrogen fluoride as a solvent. When hydrogen cyanide is employed as the nitrile, no imidoyl fluorides are obtained but, instead, novel N,N'-dialkyl-2-alkylaminomalonamides are isolated in low yield.

The Ritter condensation between an olefin and nitrile in liquid hydrogen fluoride was discussed in the preceding paper;² however, little emphasis was placed on the nature of the reaction intermediate. Since the initial suggestion of Ritter and Minieri³ of an intermediate iminosulfate **1** in the condensation of olefins or alcohols with nitrile to produce amides in sulfuric acid systems, numerous reports have appeared concerning attempts toward its isolation,^{4,5} kinetic data⁶ to establish its existence, and mere speculation^{7,8} on its intermediacy. Recently Glikmans, *et al.*,⁴ have reported isolating the iminosulfate intermediate **1** from



the reaction of isobutylene with acrylonitrile in an acetic-sulfuric acid mixture.

Since hydrogen fluoride is much more volatile (bp 19.6°) than sulfuric acid and readily effects the condensation of an olefin and nitrile,² it was found that



the novel intermediate imidoyl fluorides **2** could be isolated in the pure state.

The properties and yields of the various imidoyl fluorides produced are listed in Table I, whereas the analytical and spectroscopic data are detailed in the Experimental Section. The reaction is carried out under anhydrous conditions since any water will instantly yield the amide and can be generalized as follows: A "secondary" olefin, *i.e.*, one not capable of forming a tertiary carbonium ion, is added under anhydrous conditions to a mixture of the nitrile and HF. The reaction is allowed to proceed from 30 min to 2 hr at 0–40° and excess HF is removed by distillation *in vacuo*. An aprotic solvent, such as ethyl ether, is added and gaseous ammonia is passed into the solution.

(1) Portions of this paper were presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) Paper I: J. R. Norell *J. Org. Chem.*, **35**, 1611 (1970).

(3) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

(4) G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1376 (1966).

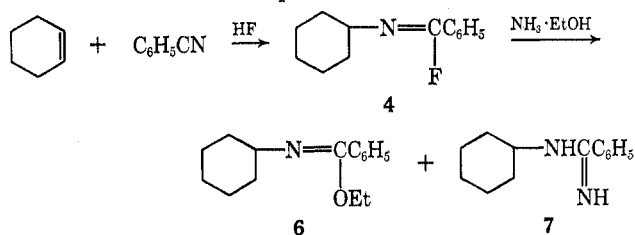
(5) T. Clarke, J. Devine, and D. W. Dicker, *J. Amer. Oil Chem. Soc.*, **41**, 78 (1964).

(6) G. Glikmans, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1383 (1966).

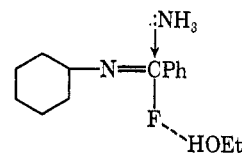
(7) J. J. Ritter, *J. Amer. Chem. Soc.*, **70**, 4253 (1948).

(8) F. R. Benson and J. J. Ritter, *ibid.*, **71**, 4128 (1949).

The precipitated ammonium fluoride is removed by filtration and the product is isolated by vacuum distillation after evaporation of the solvent. Care must be exercised during the reaction, work-up, and storage to maintain anhydrous conditions because of the tendency of imidoyl fluorides toward hydrolysis. In the case of N-cyclohexylbenzimidoyl fluoride (**4**), when a protic solvent, such as ethanol, is employed in place of ether prior to neutralization, a mixture of imido ester **6** and amidine **7** is formed. No imidoyl fluoride is observed. However, using ether, good yields (50–70%) of **4** are obtained. A possible rationalization is that



the fluorine, by hydrogen bonding, combines with the proton in ethanol thus weakening the C–F bond and facilitating nucleophilic attack by ammonia. No such solvating effect exists with ether which enables a facile isolation of **4**.



Cyclohexene reacts with acetonitrile to form N-cyclohexylacetimidoyl fluoride (**3**), a very reactive, fuming liquid. It attacks glass, stopcock grease, and metal cap liners and appears to attack stainless steel needles during glpc analysis. Extreme care and speed is required to obtain a satisfactory analysis because the product is hydrolyzed by moisture in the air to N-cyclohexylacetamide and HF.

1-Pentene, an example of a linear olefin, reacted with benzonitrile to produce N-pentylbenzimidoyl fluoride (**5**). Although the product should exist as a mixture of the 2 and 3 isomers,² the proton nmr spectrum indicated mostly the 2 isomer. The ¹⁹F nmr spectrum displayed two singlet peaks which may be interpreted as "syn" and "anti" isomers of the imidoyl fluorides.

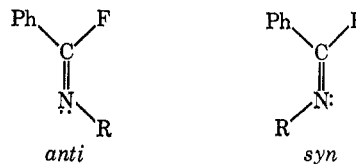


TABLE I
 IMIDOYL FLUORIDES FROM OLEFINS AND NITRILES

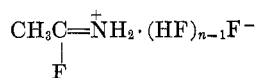
No.	Compound	Olefin	Nitrile	Yield, %	Bp (mm), °C	n_D^{20}
3	N-Cyclohexyl-acetimidoyl fluoride	Cyclohexene	CH ₃ CN	33	40-42 (4.0)	1.4390
4	N-Cyclohexyl-benzimidoyl fluoride	Cyclohexene	C ₆ H ₅ CN	59	89-92 (0.55)	1.5268
5	N-(2- and 3-pentyl)-benzimidoyl fluoride	1-Pentene	C ₆ H ₅ CN	62	53-62 (0.25)	1.4960
		2-Methyl-2-butene	C ₆ H ₅ CN	0		
		Cyclohexene	HCN	0		

 TABLE II
 REACTION PARAMETERS AND YIELD DATA FOR N,N'-DIALKYL-2-ALKYLAMINOMALONAMIDES

Olefin	Olefin, mol	HCN, mol	HF, mol	Olefin addn time, min	Reaction time, hr	Temp, °C	Purified yield, %	Recryst solvent	Mp, °C	Compd no.
Propylene	1.1	1.2	8.0	12	2.0	50	23.3	Pentane	103-104	9
Cyclopentene	1.0	1.2	8.0	35	2.5	44-50	10	Hexane	126-128	10
Cyclohexene	2.0	2.4	8.0	38	4.0	45	19.4	85% Me ₂ CO	120-122	8
Cyclododecene	1.0	1.2	10.0	52	2.0	50	14.0	Isopropyl ether-benzene	153-154.5	11
1-Pentene	1.0	1.2	8.0	42	2.0	45-50	3.9	Hexane	76-78	12
Norbornene	0.5	0.6	4.1	37	5.0	0-20	10.6	Hexane-EtOH	180.5-182	13

No imidoyl fluorides were obtained using a "tertiary" olefin, such as 2-methyl-2-butene. This observation supports our earlier premise² that for tertiary carbonium ions dilute acid is required for amide formation because of the reversibility of the reaction forming the intermediate imino cation. In strong acid the imidoyl fluoride tends to revert to the more stable tertiary carbonium ion which then polymerizes or fragments, whereas, when the system contains water, the imino carbonium ion or fluoride is trapped as the enol and yields the amide.

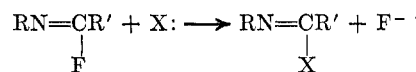
The imidoyl fluorides are essentially an unknown class of compounds; however, N-*n*-butyl- α -chloro- α -fluoroacetimidoyl fluoride has been reported by Pruett, *et al.*,⁹ as arising from an addition of *n*-butylamine to chlorotrifluoroethylene followed by elimination of HF. Wiechert, *et al.*,¹⁰ have reported that condensation of HF and acetonitrile at 100° forms a complex saltlike material which they postulate to be



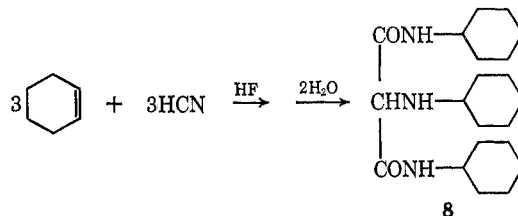
No analysis or thorough characterization was obtained nor was the free base isolated. Most recently, Merritt and Johnson¹¹ have reported the transient existence of N-(2-pentyl)benzimidoyl fluoride arising from the elemental fluorination of benzilidene-2-pentylamine. The compound was observed only in the crude state by nmr and could not be isolated by their technique.

In general the chemistry of imidoyl fluorides should resemble that of the imidoyl chlorides, but the fluorides

are probably more resistant to hydrolysis and other forms of nucleophilic attack. Analogous to the chlorides, alkyl imidoyl fluorides are less stable than the aryl derivatives. In addition to hydrolysis to amides (Ritter-type reaction), these compounds should readily form imino ethers, amidines, thioamides, etc., and under proper conditions react with most nucleophiles.



Noteworthy in the foregoing discussion is that no imidoyl fluorides were isolated from the reaction of HCN and an olefin in HF. During our early studies of imidoyl fluorides only "tar" was obtained in reactions with HCN. It was later found that white crystals could be isolated which were identified as N,N'-dialkyl-2-alkylaminomalonamides. The reaction has the following stoichiometry: 3 mol of olefin, 3 mol of HCN, and 2 mol of water combine to form the malonamide, which for cyclohexene is formulated as follows.



Reaction conditions follow: 0-50° for 1-2 hr using 8-10 mol of HF, 1.0-2.5 mol of olefin, and a slight molar excess of hydrogen cyanide. Table II lists the olefins which underwent reaction, with the properties of

(9) R. L. Pruett, *et al.*, *J. Amer. Chem. Soc.*, **72**, 3646 (1950).

(10) K. Wiechert, H. H. Heilmann, and P. Mohr, *Z. Chem.*, **3**, 308 (1963).

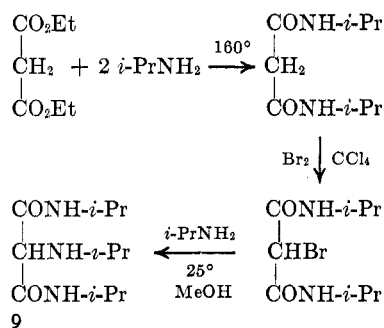
(11) R. F. Merritt and F. A. Johnson, *J. Org. Chem.*, **32**, 416 (1967).

the resulting *N,N'*-dialkyl-2-alkylaminomalonamides. Yields are low, *ca.* 20% maximum; however, the crude yields are all quite high. In most cases the reaction was not run to optimize purified yields but rather to explore its scope, and the products were isolated by repeated crystallizations from the tars.

As Table II illustrates, identifiable adducts were obtained with propylene, cyclopentene, cyclohexene, cyclododecene, 1-pentene, and norbornene. Under the specific conditions employed, no adduct was isolated from the reaction of 1-octene and 7-tetradecene, although the infrared spectra of the reaction products indicated the presence of amides. No product was isolated from the reaction of ethylene, under the conditions employed, although some ethylene was absorbed. 2-Methyl-2-butene, a tertiary olefin, did not yield any malonamide, which is not too surprising from our work on attempted isolation of imidoyl fluorides from such olefins. This is probably due to relative stabilities of intermediate carbonium ions and reversible processes occurring as was explained earlier.² 4-Vinyl-1-cyclohexene gave extensive formation of higher molecular weight products.

An attempt was made to determine if the new synthesis could be used with sulfuric acid in place of hydrogen fluoride. It was found, however, in a nearly disastrous circumstance, that liquid HCN and H₂SO₄ are not compatible under our conditions. At 0° the two materials can be mixed without any noticeable reaction; however, when removed from the ice bath, the mixture will slowly warm to 30–40°. Once this temperature is attained the mixture suddenly heats to about 140° with almost explosive force.¹²

As described in the Experimental Section, proof of structure was based on an elemental analysis and infrared, nmr, and mass spectroscopy. In the case of propylene, *N,N'*-diisopropyl-2-isopropylaminomalonamide (9) was independently synthesized by the following series of reactions.



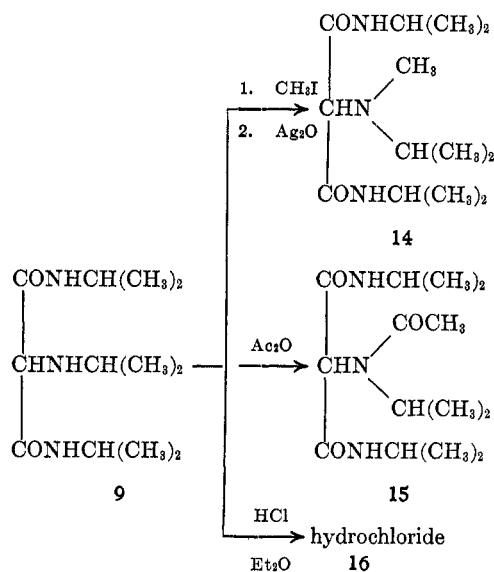
Compound 9 could not be prepared directly from diethyl bromomalonate and 3 mol of isopropylamine because of complex condensations which are known to occur.¹⁵

(12) This observation is not well documented in the literature or in monographs on hydrogen cyanide. Normally strong acids are thought to stabilize HCN and bases will promote a dangerous polymerization reaction. In a major source book¹³ on HCN a chapter is devoted to the action of strong mineral acids on nitriles and only a reference is made to an old article on the interaction of HCN–H₂SO₄ with no implications as to its hazards. The early reference,¹⁴ however, cites this rapid heat buildup which we observed. No such heating was noted with HCN and HF.

(13) V. Migridichian, "The Chemistry of Organic Cyanogen Compounds," ACS Monograph Series, No. 105, Van Nostrand-Reinhold Co., Princeton, N. J., 1947, p 57.

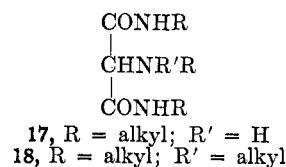
(14) A. W. Cobb and J. H. Walton, *J. Phys. Chem.*, **41**, 351 (1937).

As part of our proof of structure the following chemical reactions were observed with 9, which in turn produced new derivatives.

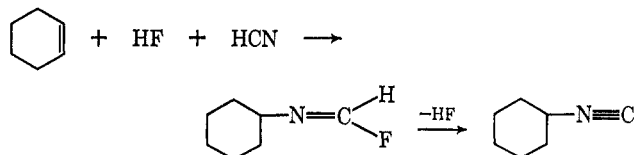


No reduction by LiAlH₄ of the amide groups on either compound 8 or 9 could be detected. The 2-alkylamino group does not undergo some of the classical tests for secondary amines such as the Hinsberg test or reaction with phenyl isothiocyanate.

Similar to the imidoyl fluorides, the substituted aminomalonamides are not a well-known class of compounds; the *N,N'*-dialkyl-2-alkylaminomalonamides have been prepared in the past by rather elaborate synthetic schemes.¹⁵ Very few compounds have been reported where the 2-amino group contains an active hydrogen, *i.e.*, arises from a nucleophilic displacement of a halogen by a primary amine on a 2-halomalonamide to form 17, but usually those such as 18 have been reported *via* displacement with secondary amines.



Several mechanisms for formation of the malonamides have been considered. We suggest the following as one plausible rationalization. In our work during a large-scale preparation of cyclohexylformamide from HF and HCN, we observed the formation of cyclohexyl isocyanide and postulated its formation as follows.²

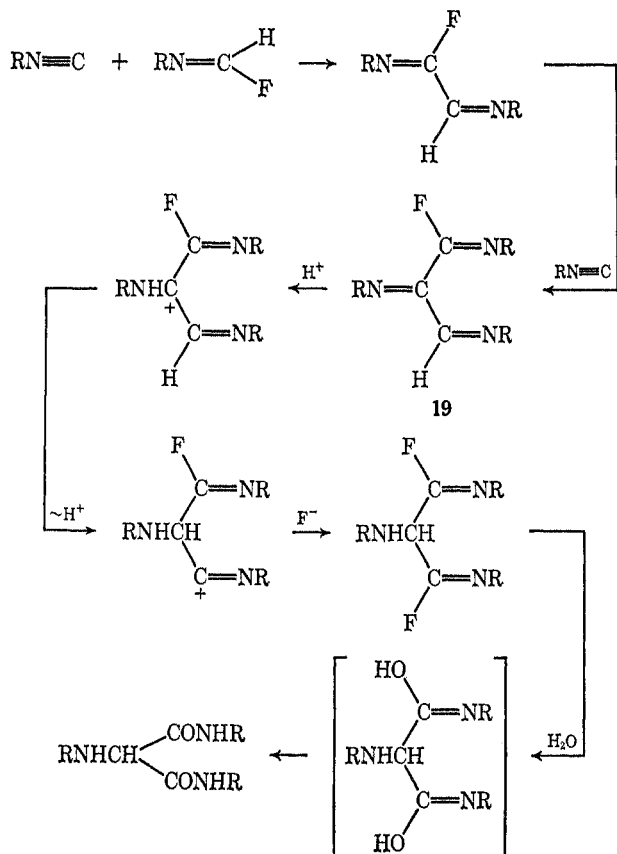


Similarly in our malonamide syntheses the odor of isocyanides is prevalent. Recently Ito, Okano, and Oder¹⁶ disclosed that isocyanides react with *N,N'*-dialkylamide chlorides to give *N,N'*-dialkyl-2-dialkyl-

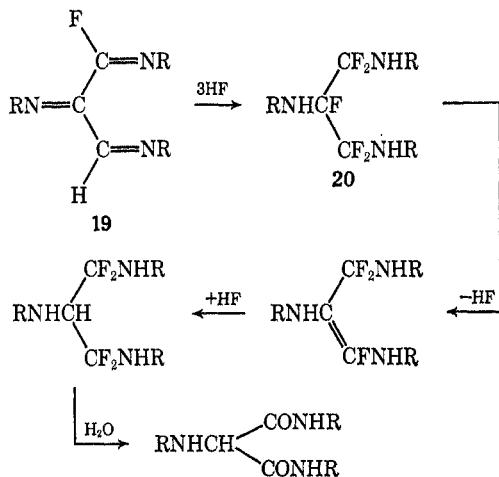
(15) (a) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **117**, 980 (1956); (b) R. W. West, *J. Chem. Soc.*, **127**, 748 (1925); (c) F. C. Uhle and L. S. Harris, *J. Amer. Chem. Soc.*, **78**, 381 (1956).

(16) Y. Ito, M. Okano, and R. Oder, *Tetrahedron*, **22**, 447 (1966).

aminomalonamides **18**. By invoking their reasoning, a similar type of mechanism involving imidoyl fluorides and isonitriles would provide a possible route to the aminomalonamides.



It is also possible that intermediate **19** could add 3 mol of HF to give **20** and then an elimination-readdition sequence could occur.



Since these reactions are carried out in anhydrous HF ($H_0 = -9.9$), such strong acidity would lead to highly cationic species involving numerous rearrangements and hydride transfers, as well as numerous protonated species not shown in the mechanism.

Experimental Section

Materials.—Colorless 99.9% hydrogen fluoride was obtained from Air Products, Inc., Allentown, Pa., and was withdrawn in the liquid phase by inverting the cylinder and taking off the HF

through Monel valves as described in our previous paper.² **CAUTION!** When handling anhydrous HF, a face shield, rubber gloves with plastic arm bands, and a protective apron are worn, using excellent hood facilities. All olefins were Phillips pure grade and the nitriles were Eastman White Label with the hydrogen cyanide being obtained from Du Pont and stabilized with P_2O_5 . The nmr spectra were obtained on a Varian A-60 spectrometer for the proton spectra and a HR-60 for ^{19}F resonance. Mass spectra were run on a high resolution CEC mass spectrometer, Model 21-110. Molecular weights were determined by osmometry and the infrared spectra were recorded on a Perkin-Elmer Infracord Model 127. Melting points were obtained on a Hoover-Thomas capillary melting point apparatus and are uncorrected.

N-Cyclohexylacetimidoyl Fluoride (3). **Run 1.**—A 300-ml Monel reactor was dried at 120° and cooled in ice under a nitrogen flow. Anhydrous HF (48.6 g, 2.43 mol) was added by means of a plastic graduate followed by CH_3CN (10.0 g, 0.26 mol). Cyclohexene (16.4 g, 0.20 mol) was added dropwise and the reactor was capped and shaken at room temperature (*ca.* 25°) for 30 min. The excess HF was removed by attaching a short piece of Monel tubing to a second 300-ml bomb immersed in Dry Ice-acetone and pulling a water-pump vacuum on the system through the second vessel to distil the excess HF. Between the second bomb and water pump a vacuum flask containing NaOH pellets was inserted to prevent any HF from escaping into the drains. Hoke valves were placed on both sides of the second bomb so that it could be easily removed and the weight of distilled HF could be determined. When this system was used and the reaction bomb was heated in warm water, a total of 36.0 g of HF was removed over a period of about 1 hr. After the vessel was cooled in ice, the pressure gauge assembly was removed under a nitrogen flow and 150 ml of ether was added. The bomb was capped and attached to a second 300-ml Monel vessel containing about 50 g of liquid ammonia at 100 psig. The two vessels were placed in a shaker, the reaction vessel was pressured slowly (to prevent overheating because of heat of neutralization) to 100 psig with NH_3 and allowed to fall to *ca.* 20 psig, and the process was repeated until no more NH_3 was absorbed. The reactor was shaken at *ca.* 30° for 1.5 hr after a total of 16 g of NH_3 had been added. The mixture was filtered under nitrogen to remove the precipitated ammonium fluoride and washed with ether. Concentration of the filtrate left 16.6 g (64% crude yield) of a fuming, bubbling liquid. Distillation of 14.1 g of the amber-colored liquid gave 8.0 g of the colorless product, bp $40-42^\circ$ (4.0 mm), with 3.4 g of residue remaining in the still pot.

The infrared spectrum (neat) showed no N—H or amide bands; however, a significant band at 5.78μ indicated the presence of the $>C=N-$ linkage. The nmr spectrum (CCl_4) was in good agreement with the assigned structure **3**: δ 1.90 (d, 3, $J = 10.5$ Hz, $=CFCH_3$), 1.48 (m, 10, ring protons), and 3.65 (m, 1, ring proton α to N). The ^{19}F resonance exhibited a well-defined quartet, 2995 cps from CF_3CO_2H giving δ_F (from CF_3CO_2H) 49.9. This compares favorably with a δ_F 52.7 for the boldface fluorine in $C_2F_7N=CFCF_3$.¹⁷

Run 2.—The reaction was repeated using 51.6 g (2.58 mol) of HF and after the reaction 34.0 g of the HF was removed. After work-up 19.0 g (66%) of the crude product was obtained which was immediately distilled in a flame-dried apparatus at 33° (2.0 mm). After the product was stored overnight in a glass-stoppered distillation receiver, it was redistilled at 34° (2.5 mm) and taken immediately to the Analytical Section. The transfer of samples for the elemental analyses was made in a drybox under a blanket of nitrogen and the analyses were run shortly after the second distillation.

Anal. Calcd for $C_6H_{14}FN$: C, 67.10; H, 9.85; N, 9.75; F, 13.3; mol wt, 143. Found: C, 66.84; H, 9.86; N, 9.70; F, 13.4; mol wt, 142 (obtained by extrapolation to infinite dilution in benzene).

The compound yellowed rapidly on standing and attacked glass, stopcock grease, polyethylene film, and metal cap liners. When shaken with 5% NaOH, N-cyclohexylacetamide precipitated, mp $105-106^\circ$ (lit.¹⁸ mp 104°).

(17) N. Muller, P. C. Lauterbur, and G. F. Svatos, *J. Amer. Chem. Soc.*, **79**, 1807 (1957).

(18) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 288.

N-(2- and 3-Pentyl)benzimidoyl Fluoride (5).—The reaction was run similarly to the foregoing experiment except that 46.4 g (2.32 mol) of HF, 20.6 g (0.20 mol) of benzonitrile, and 14.0 g (0.20 mol) of 1-pentene were used with 30.0 g of the HF being removed by distillation after the reaction was completed. In this case 13 g of ammonia was pressured into the reactor and ether (150 ml) was added followed by an additional 8 g of NH_3 . The solution was filtered and concentrated to give 32.5 g (83% crude) of an amber-colored nonviscous oil. The infrared spectrum showed a trace of N—H and a small amount of —CN indicative of unreacted benzonitrile as well as the characteristic C=N band at 5.78μ . Distillation gave 23.3 g (62% yield) of colorless product, bp $53\text{--}62^\circ$ (0.25 mm); the distillation residue weighed 2.5 g. For analysis the product was redistilled at $54\text{--}55^\circ$ (0.20 mm), n_D^{20} 1.4960.

Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{FN}$: C, 74.57; H, 8.34; F, 9.83; N, 7.25; mol wt, 193. Found: C, 74.37; H, 8.52; F, 9.70; N, 7.25; mol wt, 196.

The fluorine nmr spectrum exhibited a strong "doublet" with $J = 43$ Hz. These peaks were of equal intensity suggesting existence of *syn* and *anti* isomerism. Proton nmr spectra indicated the product was mostly N-2-pentylbenzimidoyl fluoride with some 3 isomer.

N-Cyclohexylbenzimidoyl Fluoride (4).—The reaction was run similarly to the foregoing experiment except that 59.5 g (3.0 mol) of HF, 20.6 g (0.20 mol) of benzonitrile, and 16.4 g (0.20 mol) of cyclohexene were used and the reaction mixture was shaken for 80 min at room temperature (30°). Following removal of the HF (40.5 g) the mixture was treated with ether and ammonia (16 g) and was shaken overnight at 30° under ammonia pressure (100 psig). Filtration and evaporation of the ether gave 35.3 g (yield, 86%) of the crude imidoyl fluoride.

A portion (22.9 g) of the crude product when distilled gave 15.8 g of a pale yellow distillate boiling at $89\text{--}92^\circ$ (0.5 mm); an analytical sample was obtained by redistillation, $87\text{--}88^\circ$ (0.4 mm), n_D^{20} 1.5268.

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{FN}$: C, 76.06; H, 7.86; F, 9.26; N, 6.82; mol wt, 205. Found: C, 76.23; H, 7.93; F, 9.25; N, 6.62; mol wt, 212 (osmometer).

The infrared spectrum indicated very little N—H and the C=N band at 5.9μ was present. The nmr spectrum (50% in CDCl_3) exhibited δ 7.5 (m, 5, aromatic protons), 1.6 (m, 10, cyclohexyl protons), and 3.9 (m, 1, CHN=CF-). Two of the aromatic protons exhibited coupling with the fluorine. The ^{19}F resonance indicated a singlet, 1682 Hz from $\text{CF}_3\text{CO}_2\text{H}$. The mass spectrum showed no parent peak; however, the cracking pattern was consistent with the assigned structure since benzonitrile and cyclohexene fragments were observed. The compound decomposed on the column when subjected to glpc analysis.

Ethyl N-Cyclohexylbenzimidate (6) and N-Cyclohexylbenzamide (7).—The reaction was carried out in apparatus similar to those described previously with 60 ml of HF, 20.6 (0.20 mol) of benzonitrile, and 16.4 g (0.20 mol) of cyclohexene being used. A total of 41.9 g of HF was removed by distillation. In place of ether, 150 ml of absolute ethanol was added and cooled to 0° . Ammonia gas was bubbled into the solution at a rate such that the temperature did not exceed 45° . A heavy precipitate formed which was filtered and washed with ethanol; concentration of the filtrate left 34.4 g of a liquid residue. This was triturated with a mixture of ether (100 ml) and acetone (200 ml) giving 8.70 g of a gummy white solid, N-cyclohexylbenzamide hydrofluoride. Dissolution in 150 ml of water followed by 50 ml of 10% NaOH liberated the free base as a precipitate and recrystallization (hexane-EtOH) gave 4.9 g of white crystalline N-cyclohexylbenzamide, mp $116\text{--}117.5^\circ$ (lit.¹⁹ mp $116\text{--}116.5^\circ$); the picrate melted at $142\text{--}143.5^\circ$ (lit.¹⁹ mp 143°).

The ether-acetone triturating solvent was evaporated to give 23.9 g of a red-brown residue which on distillation gave 12.9 g of ethyl N-cyclohexylbenzimidate (6) as a colorless liquid, bp $105\text{--}109^\circ$ (0.6 mm), n_D^{20} 1.5189.

The infrared spectrum (Nujol) indicated the following: 6.02 ($>\text{C}=\text{N}$), 6.29 (aromatic), and 9.05μ (ROR) with no bands present at 3.0μ describing the absence of N—H bonds. The nmr spectrum (30% in CDCl_3) exhibited δ 7.30 (s, 5, aromatic protons), 4.22 (q, 2, $-\text{OCH}_2\text{CH}_3$) 3.18 (m, 1, ring H α to N), and 1.52 and 1.28 (m and t, 13, cyclohexyl protons and $-\text{OCH}_2\text{CH}_3$).

(19) P. Oxley and W. F. Short, *J. Chem. Soc.*, 449 (1949).

Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}$: C, 77.88; H, 9.15; N, 6.05; mol wt, 231. Found: C, 77.76; H, 9.40; N, 6.20; mol wt, 230.

Reaction of 2-Methyl-2-butene with Benzonitrile in HF.—The reaction was run similarly to the preceding experiment except that 47.4 g of HF, 20.6 g (0.20 mol) of 2-methyl-2-butene, and 20.6 g (0.20 mol) of benzonitrile were employed. After the mixture was shaken for 30 min at 30° , the HF was removed with a resultant loss in weight of 58 g. This loss was 10.6 g more than the original amount of HF added indicating loss of 2-methyl-2-butene or *t*-amyl fluoride. The yellow residue in the reaction vessel was poured on ice, neutralized with NH_4OH , and extracted with ether. Removal of the ether left 20.9 g of a yellow residue, which by glpc analysis indicated mostly benzonitrile with traces of oligomers. By the foregoing procedure, no evidence for imidoyl fluoride formation was noted. The HF that was distilled into the second bomb was worked up similarly and was found to contain 8.2 g of benzonitrile and oligomers of 2-methylbutene indicative of free 2-methyl-2-butene or *t*-amyl fluoride being flashed over and subsequently polymerizing.

N,N'-Diisopropyl-2-isopropylaminomalonamide (9).—Hydrogen fluoride (160 ml, 8.0 mol) was placed in a 300-ml Monel reactor and cooled in ice water; addition of liquid hydrogen cyanide (48 ml, 33 g, 1.22 mol) followed. The reactor was capped and pressured with N_2 (ca. 150 psig) and the contents were transferred into a 1-l. Monel autoclave by means of a dip tube. Propylene (45 g, 1.07 mol) was condensed in a stainless steel bomb, which was fitted to the large reactor. Propylene, at 150 psig, was bled into the HF-HCN mixture at $23\text{--}29^\circ$ with vigorous stirring over a period of 12 min. The autoclave was heated to 50° and stirred an additional 2 hr. After cooling, 300 ml of water followed by 200 ml of CH_2Cl_2 were pumped into the autoclave for an "in situ extraction." After being stirred an additional 15 min, the contents were drained into a polyethylene separatory funnel and the HF-H₂O layer extracted once with 150 ml of CH_2Cl_2 . The combined CH_2Cl_2 layers were made basic with aqueous NaOH, dried over MgSO_4 , and concentrated to give 6.1 g of a foul-smelling yellow oil which was discarded. The initial HF-aqueous layer was made basic with 40% NaOH and allowed to stand overnight. Silky crystals formed which when filtered and air dried gave 45.3 g (53% crude yield) of yellow solids. The material was recrystallized once from 200 ml of 75% acetone-25% water and then twice from 200 ml of pentane to give two crops of crystals; 10.95 g, mp $102.5\text{--}104^\circ$, and 9.29 g, mp $103\text{--}104^\circ$, for a total yield of 20.24 g (23.3% yield).

The product is soluble in pentane and very soluble in CCl_4 , MeOH, EtOH, dilute HCl, pyridine, C_6H_6 , CHCl_3 , and Et_2O . It is soluble in hot water after a few drops of EtOH have been added and is insoluble in dilute NaOH.

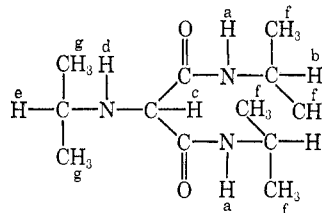
Structure Determination. The structure of compound 9 was determined in the following manner.

Anal. Calcd for $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_2$: C, 59.23; H, 10.36; N, 17.27; O, 13.2; mol wt, 243. Found: C, 59.08; H, 10.44; N, 16.93; O, 12.9; mol wt, 257; equiv wt, 243 (when titrated with $\text{HClO}_4\text{--HOAc}$).

A. Spectroscopic Data.—The nmr spectrum (described in Table III) provides a clear picture of the structure.

TABLE III

Proton	Chemical shift, δ	Appearance	Obsd no. of protons	No. of protons required
a	7.4-7.8	Broad singlet	2.0	2
b	3.8-4.2	Heptet	2.0	2
c	3.6	Singlet	1.0	1
d	2.7-2.9	Broad multiplet	2.0	1
e	2.7-2.9	Broad multiplet		
f	1.1-1.3	Doublet	18.0	12
g	1.0-1.2	Doublet } overlapping		



Protons a and d are active protons as required by the structure since addition of D₂O to a solution of the sample in acetone-d₆ causes the corresponding peaks to shift to τ 5.2 because of rapid exchange with D₂O.

The infrared spectrum (Nujol) exhibited 6.08 and 6.12 (C=O), 3.08 (N—H), and other medium bands at 3.25, 6.50, 7.98, 8.58, and 11.67 μ .

B. Chemical Reactivity Data. 1. Reaction with Methyl Iodide.—Compound 9 (1.5 g) was heated at reflux in 20 ml of methyl iodide for 18 hr, giving a yellow solution which on evaporation left a crystalline mass. Recrystallization from hexane-ethanol gave 1.54 g of yellow crystals, mp 204–205°.

Anal. Calcd for C₁₈H₂₈IN₃O₂: C, 40.53; H, 7.32; N, 10.91. Found: C, 40.26; H, 7.47; N, 10.67.

The iodide salt (1.4 g) was dissolved in 30 ml of H₂O and 2 g of freshly prepared Ag₂O was added. The slurry was stirred at room temperature for 2 hr. Filtration, water washing, extraction with ether, and drying over MgSO₄ gave 14 (white crystals) which melted at 132–133° after recrystallization from *n*-hexane. Analysis indicated addition of one methyl group.

Anal. Calcd for C₁₉H₂₇N₃O₂: C, 60.66; H, 10.58; N, 16.33; mol wt, 257. Found: C, 60.60; H, 10.64; N, 16.24; mol wt, 244.

2. Acetylation.—Compound 9 (1.0 g) was heated at 100–110° with 15 ml of acetic anhydride for 3 hr. The solution turned dark red-brown. Excess Ac₂O was removed *in vacuo* and the residue was heated in hot hexane. The mixture was filtered and cooled to give brownish crystals; a second recrystallization from hexane gave 15 (white crystals), mp 125–126°. Analysis indicated the introduction of one acetyl group.

Anal. Calcd for C₁₄H₂₇N₃O₃: C, 58.92; H, 9.54; N, 14.72. Found: C, 58.74; H, 9.55; N, 14.76.

3. HCl Salt.—Compound 9 (1.0 g) was dissolved in 100 ml of ether and anhydrous HCl was bubbled into the solution, forming a fine precipitate. Nitrogen was swept through the system to remove the excess HCl. Filtering and drying gave 1.1 g of the very finely powdered hydrochloride 16, mp 266–267° dec.

Anal. Calcd for C₁₂H₂₅ClN₃O₂: C, 51.51; H, 9.37; N, 15.02. Found: C, 51.28; H, 9.30; N, 14.62.

4. Sodium Hydroxide Fusion.—When a small portion of the adduct was placed in powdered NaOH and heated, isopropylamine evolved.

C. Independent Synthesis of 9. a. N,N'-Diisopropylmalonamide.—Diethyl malonate (32.0 g, 0.20 mol) and isopropylamine (100 g, 1.7 mol) were placed in a 300-ml Monel reactor and heated at 160° (275 psig developed) for 20 hr. The excess liquid was removed *in vacuo* leaving a 36.8 g (99% crude) of pale greenish white solids. Recrystallization from *n*-hexane-ethanol gave 22.7 g of white crystals, mp 117–119°, 61% purified yield (lit.²⁰ mp 114°).

Anal. Calcd for C₉H₁₅N₂O₂: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.30; H, 9.63; N, 15.00.

b. 2-Bromo-N,N'-diisopropylmalonamide.—N,N'-Diisopropylmalonamide (9.3 g, 0.50 mol) dissolved in 50 ml of HOAc was heated to reflux and Br₂ (8.2 g, 0.05 mol) in 25 ml of HOAc was added dropwise. Heating was continued for 2 hr. After cooling and concentration, a portion of the residue was recrystallized (hexane-EtOH) to give 6.3 g, mp 200–202°, of product (lit.²⁰ mp 204°). An additional recrystallization of the residue gave 1.4 g of product of lower purity, mp 195–197°. The total yield was 7.7 g (58%).

Anal. Calcd for C₉H₁₇BrN₂O₂: C, 40.77; H, 6.46; N, 10.56. Found: C, 40.90; H, 6.44; N, 10.12.

c. Compound 9.—Methanol (60 ml), isopropylamine (18 g, 0.3 mol), and 2-bromo-N,N'-diisopropylmalonamide (6.0 g, 0.02 mol) were placed in a 300-ml Monel reactor. The reactor was capped and shaken for 15 hr at room temperature. The mixture was evaporated to dryness and made basic with 3% NaOH, and the precipitated solids were filtered and washed with water. Recrystallization from *n*-pentane yielded two small crops of white crystals which totaled less than 1 g, mp 103–104°.

A mixture melting point with the product obtained from propylene, HCN, and HF showed no depression (mp 103.5–104.5°). The infrared spectrum (Nujol) and the nmr spectrum of the independently synthesized material were completely superimposable on the spectrum from the HCN–HF–propylene product.

N,N'-Dicyclohexyl-2-cyclohexylaminomalonamide (8).—A 1-l. Monel autoclave was charged with a mixture of HF (160 g, 8.0

mol) and HCN (66 g, 96 ml, 2.4 mol) and then was pressurized with N₂ to 800 psig. Cyclohexene (164 g, 2.0 mol) was pumped into the reactor over a period of 38 min at 20° and the mixture was heated at 45° for 4 hr with vigorous stirring. The mixture was cooled, CH₂Cl₂ (250 ml) was pumped into the reactor, and the contents were drained into an ice bath. After this mixture was stirred vigorously, the bottom organic layer was made basic by shaking with NaOH solution and dried over MgSO₄. Concentration gave 258.4 g of a viscous red-brown tar. To obtain a crystalline material from this residue is strictly an art and the description below points out the conditions which we found to be most satisfactory. The initial residue was chilled in a refrigerator for 2–4 hr and then allowed to stand at room temperature until it crystallized which usually took at least 1.5 days. Seeding seemed to make the crystals form faster. The solidified mass was triturated with 85% acetone–15% water and placed in a beaker and chilled. The mixture was filtered and washed with small amounts of cold 85% acetone. The solids were dried, preferably by pressing between paper towels, and then air dried. Recrystallization of the tan solids from 85% acetone gave 47.0 g (0.13 mol or 19.4% yield) of 8: mp 120–122°; uv max (cyclohexane) 238 μ ($\epsilon \approx 150$); ir (CHCl₃) 2.82 (sh, N—H), 3.10 (N—H), 6.10 (C=O), and 6.49 μ (C=O); nmr (CDCl₃) δ 7.6–7.9 (m, 2, —CONH—), 3.5–3.9 (m, 2, ring protons α to amide), 3.68 (s,

1, —COCHCO—), 2.8–3.0 (m, 1, amino proton), 2.8–3.0 (m, 1, ring H α to amino group), and 7.5–9.0 (m, 30, ring protons).

Anal. Calcd for C₂₁H₃₇N₃O₂: C, 69.38; H, 10.26; N, 11.56. Found: C, 69.44; H, 10.54; N, 11.90; mol wt, 344.

A. Chemical Reactivity Data. 1. Acetylation.—Ac₂O (15 ml) and 8 (1.5 g) were heated at reflux for 3 hr. The excess Ac₂O was removed *in vacuo* and the residue was poured on ice. Ether was added which formed a crystalline precipitate at the interface. These crystals were of high purity, mp 175–177°, and represented introduction of one acetyl group.

Anal. Calcd for C₂₃H₃₉N₃O₃: C, 68.15; H, 9.65; N, 10.36. Found: C, 67.90; H, 10.04; N, 10.25.

2. Acid Hydrolysis.—Compound 8 (8.0 g) was dissolved in 150 g of 60% H₂SO₄ and heated at 130° for 3 days. The solution was greenish black and clear; extraction with CH₂Cl₂ gave no residue. The mixture was poured on cold concentrated NaOH with care being taken so that the temperature was never above 40°. When the mixture was strongly basic it was extracted with ether and dried over MgSO₄–K₂CO₃. Removal of the solvent left 2.7 g of cyclohexylamine which was confirmed by ir and glpc, on comparison with an authentic sample.

N,N-Dicyclopentyl-2-cyclopentylaminomalonamide (10).—A 1-l. autoclave was charged with 160 ml (8.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN and pressured to 1000 psig with CO. Cyclopentene (68 g, 1.0 mol) was pumped into the stirred reactor at a rate of 3–4 ml/min over a period of 35 min at 20–22°. The reactor was heated to 44–50° and stirred 2.5 hr. No drop in pressure was noted. The reactor was cooled to 22°, the pressure was released, and 300 ml of H₂O and 200 ml of CHCl₃ were pumped into the reactor. After drainage into plastic separatory funnels, the aqueous acid layer was extracted twice with CHCl₃ and the extracts were combined with the CHCl₃ layer initially pumped into the reactor. The aqueous layer was discarded and the red-brown CHCl₃ layer was poured on ice and made basic with NaOH solution. An emulsion formed and filtration was necessary to produce a workable mixture. The CHCl₃ layer was dried over MgSO₄ and removal of the solvent left 95.3 g of a very dark oil which tended to crystallize on standing. An analytical sample was prepared by triturating 16.0 g of the residue in 5 ml of 90% acetone and filtering to give 2.55 g of crystals which, when recrystallized from hexane, gave 1.70 g of 10, mp 126–128°.

Anal. Calcd for C₁₈H₃₁N₃O₂: C, 67.23; H, 9.73; N, 13.08; mol wt, 321. Found: C, 67.12; H, 10.22; N, 13.11; mol wt, 319 (osmometer).

N,N'-Dicyclododecyl-2-cyclododecylaminomalonamide (11).—A 1-l. autoclave was charged with 200 ml (10.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN. Cyclododecene (85% pure from Columbia Organic Chemicals Co.; the remaining 15% was cyclododecane and cyclododecadiene) (166 g, 1.0 mole) was pumped into the reactor at 16° over a period of 52 min. The mixture was heated with stirring at 50° for an additional 2 hr. The reactor was cooled and 300 ml of H₂O was added followed by 200 ml of CH₂Cl₂. The mixture was drained from the reactor and extracted further with CH₂Cl₂. Solvent removal left 204.7 g of

red-brown solids possessing a waxy appearance. The residue was suspended in acetone and filtered, the solids were then further leached of impurities with hexane (100 ml), and absolute EtOH (500 ml) was added to the boiling suspension. Cooling and filtration gave 56.7 g of buff-colored solids, mp 152–155°.

Recrystallization was effected by suspending the solid in isopropyl ether (600 ml), heating the suspension to boiling, and adding benzene dropwise to the hot solution until solution was complete. When this was cooled, 28.5 g of off-white crystals were obtained, mp 153–154.5°, representing a 14% yield; however, no attempts were made to optimize the yield.

Anal. Calcd for $C_{25}H_{37}N_3O_2$: C, 76.04; H, 11.94; N, 6.83; mol wt, 616. Found: C, 76.13; H, 12.06; N, 6.72; mol wt could not be determined because of insolubility in the available solvents.

N,N'-Dinorbornyl-2-norbornylaminomalonomide (13).—A 1-l. Monel beaker with a polyethylene cover containing apertures for an addition funnel and thermometer and provided with a magnetic stirrer was charged with 80 ml (4.0 mol) of HF and 25 ml (17.2 g, 0.64 mol) of HCN and cooled in an ice bath to 0°. Norbornene (47.0 g, 0.50 mol) was added by means of a spatula over a period of 37 min. Five hours later, 150 ml of water was added followed by 100 ml of CH_2Cl_2 . The CH_2Cl_2 layer was shaken with dilute NaOH until neutral, and removal of the solvent left 60.0 g of a viscous amber liquid. A portion of the material was triturated with 85% acetone to give 13 which, when recrystallized from *n*-hexane and ethanol, melted at 180.5–182°. A total of 7.1 g of product was obtained.

Anal. Calcd for $C_{24}H_{37}N_3O_2$: C, 72.14; H, 9.33; N, 10.52; mol wt, 399.6. Found: C, 71.94; H, 9.32; N, 10.23; mol wt, 419.

The infrared and nmr spectra were consistent with the structure postulated.

N,N'-Dipentyl-2-pentylaminomalonomide (12).—A 1-l. Monel autoclave was charged with 160 ml (8.0 mol) of HF and 33 g (48 ml, 1.2 mol) of HCN. 1-Pentene (70 g, 1.0 mol) was pumped into the reactor at 18° over a period of 42 min. It was then heated at 45–50° for 2 hr; the heating was followed by cooling and addition of 300 ml of water and 200 ml of CH_2Cl_2 . The CH_2Cl_2 layer was collected and the aqueous acid layer was extracted with CH_2Cl_2 . The organic layers were combined and shaken with NaOH–H₂O giving an emulsion which was broken by filtration. Removal of the CH_2Cl_2 after separation and drying over

$MgSO_4$ gave 90.4 g of a brown viscous liquid. Crystallization was achieved by immersing the flask in ice and adding 150 ml of hexane. Filtration and two additional crystallizations (hexane) gave a total of 4.2 g of white crystals, mp 76–78°.

Anal. Calcd for $C_{15}H_{27}N_3O_2$: C, 66.01; H, 11.39; N, 12.83; mol wt, 327. Found: C, 66.16; H, 11.42; N, 12.86; mol wt, 324 (osmometry).

Reaction of Ethylene with HCN–HF.—The 1-l. autoclave was charged with 160 ml of HF and 50 ml of HCN and pressured to 500 psig (39 g) with ethylene. The mixture was heated at 50° for 3 hr and the pressure dropped to 280 psig at 51°. It was pressured to 500 psig (21 g) and stirred an additional 1 hr. Work-up was similar to those described previously with only 2.5 g being obtained on various extractions with CH_2Cl_2 . Possibly the product which would arise would be very water soluble and not be extractable by these methods.

Reaction of 1-Octene with HCN–HF.—When 160 ml of HF, 48 ml of HCN, and 112 g (1.0 mol) of 1-octene were used under conditions described above, 139.5 g of a dark viscous residue was obtained. No identifiable materials, except a small amount of *N*-octylformamide, could be detected either by crystallization or distillation procedures.

Reaction of 2-Methyl-2-butene with HCN–HF.—Using 160 ml of HF, 48 ml of HCN, and 70.0 g (1.0 mol) of 2-methyl-2-butene under conditions described above, 30.5 g of a black tar was isolated. No identifiable products could be isolated.

Registry No.—Hydrogen fluoride, 7664-39-3; **3**, 23604-71-9; **4**, 23604-72-0; **5** (2-pentyl), 23604-73-1; **5** (3-pentyl), 23604-84-4; **6**, 23604-74-2; **8**, 23604-75-3; **8** (acetylated), 23604-76-4; **9**, 23604-77-5; **9** (methiodide), 23758-69-2; **10**, 23604-78-6; **11**, 23604-79-7; **12**, 23604-80-0; **14**, 23604-81-1; **15**, 23604-82-2; **16** (HCl), 23604-83-3.

Acknowledgment.—The author wishes to acknowledge the capable laboratory assistance of Mr. Bill Loffer and is indebted to Dr. D. S. Weinberg for assistance in obtaining and interpreting some of the spectra cited.

Crystal Structure of 10-Methylisalloxazinium Bromide Dihydrate

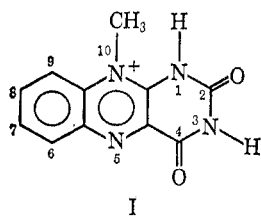
R. B. BATES, T. C. SNEATH, AND D. N. STEPHENS

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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The title compound, a model for protonated riboflavin, exists in the crystal in the tautomeric form I. There is minor deviation from coplanarity in the ring system, with a slight general bow along the long axis. The molecules are arranged in sheets of P_g symmetry with intrasheet hydrogen bonding.

In spite of the importance of riboflavin and its derivatives FMN and FAD in biological redox systems, bond parameters have been measured on only a few substances containing the riboflavin ring system.¹ This is undoubtedly due to the failure of many derivatives of interest to form crystals suitable for X-ray study. The title substance, however, which contains the cation depicted below, forms excellent crystals,



and we wish to report the results of an X-ray study on them.²

Experimental Section

Cooling of a solution of 10-methylisalloxazine in concentrated hydrobromic acid gave many-faceted, olive green crystals of 10-methylisalloxazinium bromide dihydrate.

Anal. Calcd for $C_{11}H_{13}N_4O_4Br$: C, 38.51; H, 3.86; N, 16.10; O, 18.54; Br, 23.89. Found: C, 38.29; H, 3.79; N, 16.24; O, 18.55; Br, 23.16.

(1) (a) P. Kierkegaard, *et al.*, *Chem. Commun.*, 288 (1967); (b) N. Tanaka, *et al.*, *Bull. Chem. Soc. Jap.*, **40**, 1739 (1967); (c) C. J. Fritchie, Jr., and B. L. Trus, *Chem. Commun.*, 1486 (1968).

(2) Fritchie and Trus^{1c} have communicated their results on the same substance, and our parameters appear to be in close agreement with theirs. Our preliminary results with this structure (not then fully refined) were reported: Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. O-149.