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Chelation as a Driving Force in Organic Reactions. IV.[1] Synthesis of α-Nitro Acids by Control of the Carboxylation–Decarboxylation Equilibrium[2]

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Treatment of primary nitroparaffins with carbon dioxide and magnesium methoxide (magnesium methyl carbonate) leads to magnesium salts of the corresponding α-nitrocarboxylic acids. These salts can be converted easily into the free nitro acids, the esters or the corresponding amino acids. The carboxylation reaction thus serves as a valuable method for synthesizing these compounds. On the basis of the contrasting behavior of nitroacetic acid toward sodium methoxide and magnesium methoxide, it is concluded that the success of the carboxylation reaction rests upon chelation of magnesium ions with the nitroacetate dianion. The first and second ionization constants of nitroacetic acid in water are reported.

Alteration of the length of a carbon chain by one unit often involves the addition or loss of carbon dioxide. Simple carboxylic acids can be synthesized and degraded by this scheme only if the strongest nucleophiles, such as Grignard reagents, are used in the carboxylation, and very drastic pyrolytic treatment in the decarboxylation. More interesting in preparative chemistry and biochemistry[4] are those bifunctional acids such as I (eq. 1) where X may be acyl, carboxyl, nitro, cyano,

$$\underset{\text{I}}{\text{R—CH(X)—CO}_2\text{H}} \rightleftharpoons \text{R—CH}_2\text{(X)} + \text{CO}_2 \qquad (1)$$

α-pyridyl, etc. Such substances can be decarboxylated with ease, and the reverse reaction can, in certain cases, be readily accomplished. This investigation is concerned with the interaction of coördinating metal ions with the acids I and their salts. The effects of such interaction on the equilibrium of eq. 1 are of primary interest.

Certain esters of this type form relatively stable coördination compounds (*e.g.*, acetoacetic ester with copper II ions[5]), but knowledge of such behavior on the part of the free acids I is fragmentary. Pedersen[6] reported that the rate of decarboxylation of nitroacetic acid was strongly influenced by the addition of salts of aluminum, copper, cadmium and other polyvalent metals. No structural evidence was obtained for the formation of chelate salts; however, the kinetic data were well explained by the assumption that coordination complexes between the nitroacetate ion and the metal ion were responsible for decreasing the concentration of the free anion, which is known to be the reactive species in decarboxylation.[6,7]

The rates of decarboxylation of oxaloacetic[8,9] and oxalosuccinic[9] acids are accelerated by aluminum, copper, zinc, iron and other polyvalent metal salts. The chelate complexes, which in these cases are more reactive toward decarboxylation than the free anions, clearly involve coördination of the metal ion with the α-keto acid grouping, which is not disrupted during decarboxylation, rather than the β-keto acid grouping.[10] These results do not, therefore, have clear implications for acids of the type I. However, in the course of these studies Kornberg, Ochoa and Mehler[9] reported that aluminum sulfate caused a profound change in the spectrum of sodium acetoacetate. This simple β-keto acid (I, X = $COCH_3$) apparently forms an aluminum chelate with an enolic structure, and its decarboxylation rate is not increased by chelation.

The present research began with a study of nitroacetic acid (I, X = NO_2), the decarboxylation of which had been so thoroughly studied by Pedersen. His experiments were carried out in aqueous solution where the reaction gave no evidence of being reversible. We used ultraviolet spectroscopy to observe the effect of different bases upon solutions of nitroacetic acid in water, methanol and ether. Following an examination of the salts derived from various cations, experiments were carried out to determine whether the stability of the chelate salts could be used to advantage in synthesis.

Results

The First and Second Ionization Constants of Nitroacetic Acid.—Solutions of nitroacetic acid in 4 *M* aqueous hydrochloric acid exhibit an absorption maximum at 274 mμ (ε 29.8) with a minimum at 256 mμ (ε 24) and strong end absorption. Solutions in 0.12 *M* aqueous sodium hydroxide exhibit an intense maximum at 275 mμ with an extinction coefficient of 11,000. Both solutions were quite stable at room temperature and therefore could be assumed to contain the free acid and the disodium salt, respectively. Dilute solutions of nitroacetic acid in pure water are virtually completely dissociated to the monoanion and hydrogen ion. Such solutions decarboxylate so rapidly at room temperature that a spectrum of the monoanion could be obtained only by observing the change, during several minutes, in the optical density of a series of solutions, each at a different wave length, and extrapolating to time zero. The resulting spectrum contained a very broad maximum in the 270–280 mμ region (ε 210), which was hardly more than a shoulder on the strong continuous absorption whose maximum occurred well below 235 mμ.

A determination of K_1 for nitroacetic acid was made by observing the spectrum at 260 mμ of solutions of different concentrations in distilled water, in the range 0.4×10^{-2} to 1.6×10^{-2} *M*. The solutions were allowed to decarboxylate during the spectral measurement and the absorbance of each solution at time zero was obtained by extrapolation. The dissociation constant, K_1, was obtained from the absorbances as outlined in Experimental. The second dissociation constant was determined in a 0.1 *M* borate buffer at

(1) Previous paper in this series: M. Stiles, *Ann. New York Acad. Sci.*, **88**, 332 (1960).

(2) (a) Taken largely from the Ph.D. thesis of H. L. F., University of Michigan, 1959. (b) Presented at the Symposium on Nitroparaffins, American Chemical Society Natl. Meeting, Atlantic City, N. J., September, 1959. (c) A preliminary account of this work has appeared: M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 505 (1959).

(3) Edgar C. Britton Fellow in Organic Chemistry (Dow Chemical Co.), 1958; International Business Machines Fellow, 1959; Union Carbide Summer Fellow, 1958; Allied Chemical and Dye Summer Fellow, 1959.

(4) For a discussion of several important biological transformations of this type, see M. Calvin and N. G. Pon, *J. Cell. Comp. Physiol.*, **54**, Suppl. 1, 51 (1959); F. Lynen, *ibid.*, **54**, 33 (1959).

(5) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, Inc., New York, N. Y., 1952.

(6) K. J. Pedersen, *Trans. Faraday Soc.*, **23**, 316 (1927); *Acta Chem. Scand.*, **3**, 676 (1949).

(7) K. J. Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

(8) H. A. Krebs, *Biochem. J.*, **36**, 303 (1942).

(9) A. Kornberg, S. Ochoa and A. Mehler, *J. Biol. Chem.*, **174**, 159 (1948).

(10) R. Steinberger and F. H. Westheimer, *J. Am. Chem. Soc.*, **71**, 1158 (1949); **73**, 429 (1951).

TABLE I
DISSOCIATION CONSTANTS OF NITROACETIC ACID IN WATER

	K_1[a]	K_1[b]	K_2
This work (23.5°)	0.0234	0.0329	1.25×10^{-9}[c]
Pedersen[d] (20.0°)	0.0264	0.0340	—
Heuberger[e]	—		10^{-9}

[a] At an ionic strength of approximately 0.01. [b] At an ionic strength of 0.10. [c] In 0.1 *M* sodium borate buffer. [d] Ref. 11. [e] Ref. 12.

*p*H 8.8, using solutions of nitroacetic acid in the concentration range 1.55×10^{-4} to 6.20×10^{-4} *M*.

The values for K_1 and K_2 are given in Table I alongside those determined by Pedersen[11] and Heuberger[12] from manometric measurements of the rates of decarboxylation.

Decarboxylation of Nitroacetic Acid and its Salts.—As a comparison of the spectrometric technique with the manometric,[6] decomposition of nitroacetic acid was first studied in aqueous solution, following the absorbance at 260 mμ. It was necessary to use buffered solutions since, at concentrations suitable for spectrometric measurements, the acid is largely, but not completely, dissociated, and the fraction ionized increases as the decomposition proceeds. In 0.1 *M* borate buffer at *p*H 8.8 the observed first-order rate constant was 0.697 min.$^{-1}$ (average of 3 runs). From the expression

$$k_{obs} = \frac{(H^+)}{(H^+) + K_2} k \qquad (2)$$

where $v = k$[monoanion]

the rate constant, k, for the decomposition of the monoanion could be calculated to be 0.121 min.$^{-1}$ at 23.5°. This value compares with 0.120 at 20° reported by Pedersen[6] for solutions of comparable ionic strength.

In sharp contrast with aqueous solutions, those of nitroacetic acid in methanol or ether are quite stable. A 0.032 *M* methanolic solution exhibited the spectrum of undissociated nitroacetic acid, and this spectrum was not detectably altered during 25 minutes, which is more than two half-lives of an aqueous solution. The stability is clearly related to the reduced acidity of the acid in these less polar solvents, for when sodium methoxide or diethylamine was added to a methanol or ether solution of the acid, the spectrum of the monoanion appeared and decomposition ensued rapidly. Figure 1 illustrates the manner in which the absorption at 275 mμ changed with time when varying amounts of sodium methoxide were added to a 0.016 *M* methanolic solution. When one or more equivalents were added the drop in absorbance followed a rapid first-order course (curve A). Smaller quantities of base caused the absorbance to change in the manner shown by curves B and C. At first the spectrum of such a solution changed little, but after a certain interval of time, a sharp break occurred and the intensity decreased rapidly. The result is understandable in terms of eq. 3 and 4. As long as any free nitroacetic acid remained in the solution the decarboxylation (3) was followed by the rapid proton transfer (4), which served to maintain a steady-state concentration of the nitroacetate ion. Only after the free acid was exhausted did the change in spectrum correspond to the decarboxylation step (3). The time interval required for the break in the curve depends upon the proportion of nitroacetic acid in the form of the anion, and hence upon the amount of base added (*vide infra*).

$$O_2NCH_2CO_2^- \longrightarrow O_2NCH_2^- + CO_2 \qquad (3)$$

$$O_2NCH^- + O_2NCH_2CO_2H \longrightarrow O_2NCH_2CO_2^- + CH_3NO_2 \qquad (4)$$

(11) K. J. Pedersen, *Kgl. Danske Videnskab. Selskab Mat. fys. Medd.*, **12**, No. 1 (1932).

(12) J. Heuberger, "Reaktionskinetische Studien an der spontanen Kohlensäureabspaltung der Nitroessigsäure," Uppsala, 1298, quoted by K. J. Pedersen, *Acta Chem. Scand.*, **3**, 676 (1949).

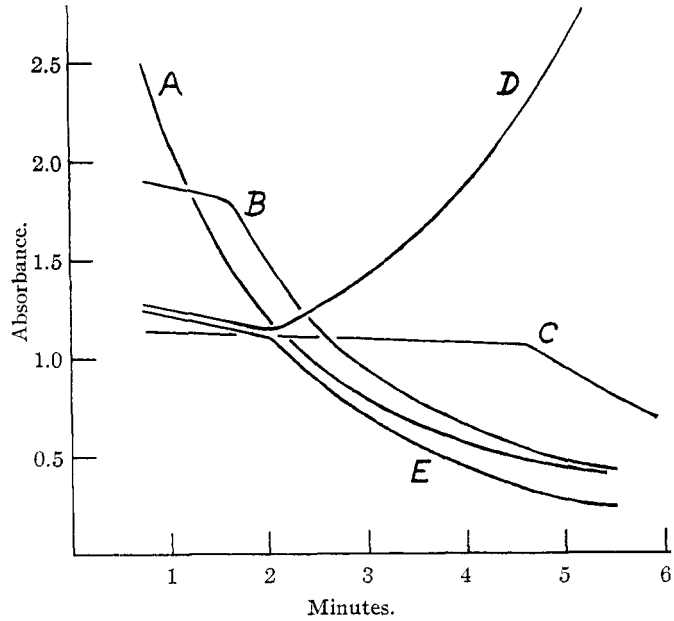


Fig. 1.—Change in absorbance (at 275 mμ) with time of solutions of nitroacetic acid in methanol containing added alkoxide. Curves, A, B and C refer to 0.016 *M* acid to which 2.0, 0.50 and 0.25 equivalents, respectively, of $NaOCH_3$ were added. Curves D and E refer to 0.011 *M* acid containing 0.55 equivalent of $Mg(OCH_3)_2$ and 0.46 equivalent of $NaOCH_3$, respectively.

Much more dramatic than the effect of solvent upon the decarboxylation rate was the effect of the metal ion. A comparison of the behavior of the sodium and magnesium salts of nitroacetic acid in methanol is made in curves D and E of Fig. 1. The two solutions contained equal quantities of acid and approximately $1/2$ the equivalent amount of sodium methoxide (E) and magnesium methoxide (D). Initially, the absorbance of each solution fell very slowly in the same way, until no undissociated acid remained; the sodium salt of the monoanion then decarboxylated, with the characteristic decay in absorbance. The magnesium salt, on the other hand, underwent a change which caused a sharp rise in spectral intensity. This change could be shown to result from the formation of the magnesium salt of the dianion, formed by the reaction of eq. 5.

$$CH_2NO_2^- + O_2NCH_2CO_2Mg^+ \longrightarrow CH_3NO_2 + O_2NCHCO_2Mg \qquad (5)$$

The neutral magnesium salt could be prepared in methanol solution by mixing together equimolar quantities of $Mg(OCH_3)_2$ and nitroacetic acid in methanol; its spectrum decreased by only 5% in intensity during 20 hours at room temperature. A solution prepared in the same way from sodium methoxide could be shown to contain no more than 4% of the nitroacetate as the dianion, even when 4 moles of methoxide per mole of acid was used, and the rate of decomposition of such a solution was approximately 10^5 times as great as that of the magnesium salt.

By use of the "method of continuous variation,"[13] it was confirmed that the stable magnesium salt was the result of reaction between nitroacetic acid and magnesium methoxide in a 1:1 ratio. A series of five solutions, each of which contained 3.0×10^{-4} *M* total concentration of reactants, was prepared with the ratio (magnesium methoxide/total) equal to 0.10, 0.275, 0.50, 0.666 and 0.875. The optical density of the five solutions was 0.30, 0.91, 1.66, 1.10 and 0.41, respectively. A plot of these values indicates the chromophore to have the composition corresponding precisely

(13) P. Job, *Ann. Chim.*, **9**, 113 (1928).

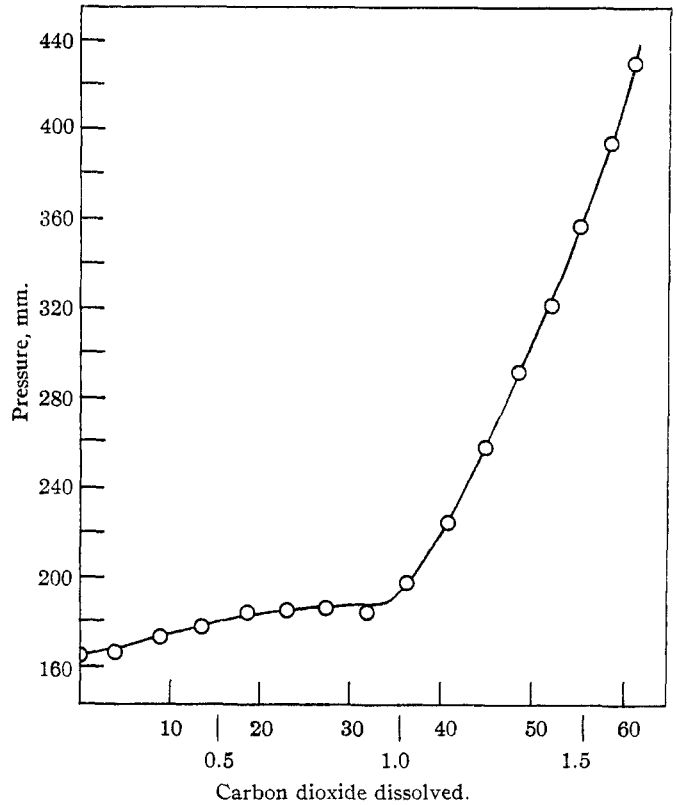


Fig. 2.—Equilibrium total pressure over 50 ml. of a solution of magnesium methoxide (0.035 mole) in methanol (30°) to which increments of carbon dioxide have been added. The abscissa is amount of dissolved CO_2 in millimoles (upper scale) and expressed as a molar ratio of dissolved CO_2 to Mg (lower scale).

to a ratio of 0.50. Attempts to crystallize the magnesium salt were not successful.

The aluminum salt of nitroacetic acid, formed by mixing aluminum isopropoxide with the acid in ether, was a white amorphous powder, insoluble in ether and methanol. Careful hydrolysis of this salt regenerated nitroacetic acid. The substance is apparently quite stable when kept dry, but it was not investigated much further because of its insolubility.

By use of the technique illustrated in Fig. 1, the rates of decomposition of the sodium, magnesium and diethylammonium salts of nitroacetic acid could be measured in methanol, and the last-named in ether as well. Variation in initial concentration of nitroacetic acid and base allowed a determination of the rate constant based upon measurement of the time, t_b (min.), required for the break (see Fig. 1) in the decomposition curve. Table II gives values for k, the first-order rate constant for decomposition of the monoanion, defined by eq. 2. The following relationship between k and t_b, where n_A and n_B denote initial concentrations of nitroacetic acid and base, is easily derived.

$$t_b = (n_A - n_B)/kn_B \qquad (6)$$

The Carboxylation of Nitroparaffins.—Magnesium nitroacetate (O_2NCHCO_2Mg), though stable in neutral methanol solution, proved very sensitive to acids. Bubbling carbon dioxide through such a solution caused fairly rapid decomposition, presumably because methyl hydrogen carbonate is sufficiently acidic to protonate the magnesium salt, producing the unstable half-salt ($O_2NCH_2CO_2Mg_{1/2}$). However, complete saturation with carbon dioxide did not destroy all of the nitroacetate. Equilibrium was reached at a point where approximately 4% of the original magnesium nitroacetate remained, as determined spectrometrically.

TABLE II

RATE CONSTANTS FOR DECARBOXYLATION OF NITROACETATES

	k, min.$^{-1}$ at 23.5°[a]		
	Water	Methanol	Ether
Na^+ salt	0.121	0.60	—
$Mg^{+2}{}_{1/2}$ salt	—	0.42	—
Mg^{+2} salt	—	$<10^{-5}$	—
$Et_2NH_2^+$ salt	—	0.63	1.45

[a] The aqueous solution contained 0.1 M sodium borate buffer; the non-aqueous solutions contained only substrate at levels of 0.001–0.01 M.

These results indicated that thermodynamics alone would not prevent the synthesis of nitroacetate from carbon dioxide, nitromethane and magnesium methoxide, although the yield achievable under these conditions could not be high.

To investigate this possibility, a solution of magnesium methoxide in methanol was saturated with carbon dioxide, and nitromethane was added. After two hours at 40° the appearance of an absorption peak at 272 mμ indicated that magnesium nitroacetate had been formed in 2.5% yield. Recovery of the free nitro acid from this dilute solution could be accomplished only with very great loss, but a sufficient quantity (*ca.* 0.5%) of the pure crystalline acid was recovered to prove beyond doubt that the reaction of eq. 1 (X = NO_2) had been successfully reversed.

Intuitively, one might expect that the carboxylation of nitromethane would proceed further toward completion at high pressures of carbon dioxide. It was quickly established that such was not the case in the system under investigation. A study of the reaction between carbon dioxide and methanolic magnesium methoxide was necessary before the nature of the carboxylation equilibrium became clear.

Figure 2 shows a plot of equilibrium total pressure in a closed system containing a solution of magnesium methoxide in methanol to which increments of carbon dioxide were added. The abscissa records values of the molar ratio of carbon dioxide to magnesium methoxide. At a ratio of less than unity, the equilibrium total pressure increases only gradually above that of pure methanol as carbon dioxide is admitted, indicating that the equilibrium of eq. 7 lies far to the right. The increase in pressure above this point is so abrupt as to suggest that the equilibrium constant for eq. 8 is

$$Mg(OCH_3)_2 + CO_2 \rightleftharpoons CH_3OMgOCO_2CH_3 \qquad (7)$$

$$CH_3OMgOCO_2CH_3 + CO_2 \rightleftharpoons (CH_3OCO_2)_2Mg \qquad (8)$$

rather small and that the species $(CH_3OCO_2)_2Mg$ predominates only at carbon dioxide pressures near one atmosphere and above.[14,15]

The extent of carboxylation of nitromethane by MMC[15] at equilibrium (eq. 9) can be expressed by eq. 10.

(14) The reports by Szarvasy[16] and Kurov[17] that the compound $(CH_3OCO_2)_2Mg$ was prepared by saturating a methanolic solution of magnesium methoxide with carbon dioxide are contrary to our experience. Passing carbon dioxide through such a solution at 25° until no further absorption could be detected produced a solution in which the ratio of acid-labile CO_2 to Mg was 1.50. Evaporation of the solvent at room temperature and reduced pressure left a solid whose analysis corresponded to $CH_3OMgOCO_2CH_3 + 0.25\ CO_2$. In one experiment carbon dioxide was bubbled through the saturated solution for 6 days without affecting the result (Dr. H. Merkl, unpublished experiments). Substitution of dimethylformamide for solvent methanol did not change the result materially; the dependence of pressure upon the CO_2/Mg ratio was closely similar to that pictured in Fig. 2 (M. D. Buckmaster, Thesis, University of Michigan, 1962).

(15) The term "magnesium methyl carbonate" (MMC) is used in this and other papers in this series to denote a solution prepared by saturating magnesium methoxide with carbon dioxide. It is clear that the composition is $CH_3OMgOCO_2CH_3 + xCO_2$, where x varies rather widely depending on solvent and temperature.

(16) E. Szarvasy, *Ber.*, **30**, 1836 (1897).

(17) V. I. Kurov, *Zhur. Obschei Khim.*, **31**, 9 (1961).

$$CH_3NO_2 + CO_2 + Hg(OCH_3)_2 \rightleftharpoons O_2NCHCO_2Mg + 2CH_3OH \quad (9)$$

$$\frac{[O_2NCHCO_2Mg]}{[CH_3NO_2]} = \frac{K[CO_2][Mg(OCH_3)_2]}{[CH_3OH^2]} = \frac{KK'[CH_3OMgOCO_2CH_3]}{[CH_3OH^2]} \quad (10)$$

Here K is the equilibrium constant for the carboxylation reaction and K' that for the reaction of eq. 7. It can be seen that the conversion is increased: (a) by an excess of MMC, (b) by elimination of methancl and (c) by increase in carbon dioxide pressure up to the point where the ratio of CO_2 to Mg in the solution is unity (and $CH_3OMgOCO_2CH_3$ is at a maximum); above this point increasing the carbon dioxide pressure has an adverse effect upon the carboxylation of nitromethane. All three of these qualitative predictions were borne out by experiment. However, a quantitative test of eq. 10 has not been possible because of the lack of information about activities in these necessarily concentrated non-aqueous solutions.[18]

The deleterious effect of methanol on the carboxylation reaction prompted a search for suitable non-protonic solvents. Both dimethylformamide (DMF) and dimethyl sulfoxide proved to be excellent solvents for MMC, and the use of these solvents, particularly DMF, opened the way to carboxylation of nitroparaffins in high yield. Suspensions of magnesium methoxide in DMF become homogeneous when saturated with carbon dioxide. Distillation of a part of the solvent is effective in removing most of the residual methanol. Subsequent resaturation with carbon dioxide at room temperature produces a solution which is stable to storage. Highest yields in the carboxylation of nitroparaffins have been obtained by treatment with at least three equivalents of MMC at 40–60° while passing a stream of nitrogen slowly through the solution. Sweeping with nitrogen is effective in keeping the partial pressure of carbon dioxide well below one atmosphere and may also aid in removing the methanol produced. Under these conditions nitromethane was converted quantitatively to magnesium nitroacetate, determined spectrometrically; careful acid hydrolysis led to the isolation of the free acid in 63% yield.[19]

Table III summarizes the results of several experiments with different nitroparaffins. In view of the difficulty in isolating the free acids, the DMF solution of the magnesium salt was treated with methanolic HCl to give the methyl ester in one case. In other examples the crude nitro acid was immediately hydrogenated to the corresponding amino acid. In every case yields refer to purified material and are based upon nitroparaffin.

Nitromethane could be carboxylated by a mixture of aluminum isopropoxide and carbon dioxide in DMF, provided a small amount of MMC (5%) was present. (The aluminum alkoxide alone is apparently not sufficiently basic to catalyze the ionization of nitromethane.) The yield of nitro acid isolated was 25%. It is therefore clear that aluminum ions can also be used to practical advantage to stabilize nitroacetate under carboxylation conditions, although this technique is less convenient.

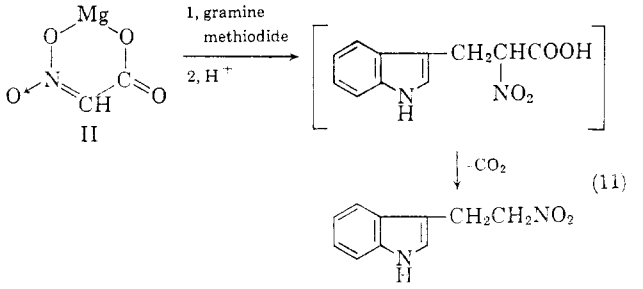
TABLE III

CARBOXYLATION OF NITROPARAFFINS BY MAGNESIUM METHYL CARBONATE

Nitroparaffin	Yield, % Nitro acid	Yield, % Amino acid
CH_3NO_2	63 (100)[a]	—
$CH_3CH_2NO_2$	49	46
$CH_3CH_2CH_2NO_2$	—	34
$CH_3CH_2CH_2CH_2NO_2$	—	42
$(CH_3)_2CHCH_2CH_2NO_2$	46[b]	—
$(CH_3)_2CHNO_2$	0[c]	—

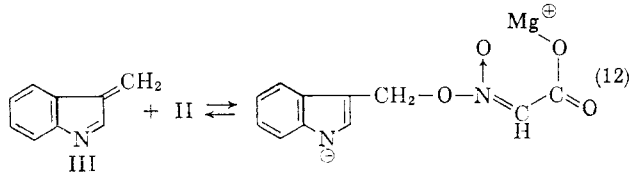
[a] By spectrometric analysis. [b] As the purified methyl ester. [c] No change in ultraviolet spectrum occurred when this nitroparaffin was treated with MMC; acid hydrolysis produced no organic acid.

Alkylation of the Magnesium Salt II.—In view of our previous success[21] in alkylating the magnesium salts of β-keto acids, numerous attempts were made to alkylate the magnesium salt of nitroacetic acid II. The only successful reaction of this type (eq. 11) was alkylation with gramine methiodide to give 3-(2-nitroethyl)-indole. Attempts to isolate the intermediate nitro acid or to reduce it to tryptophan without isolation were unsuccessful.



(11)

Treatment of II with benzyl bromide or methyl iodide led only to oxidation of the halide to the corresponding aldehyde. Similar results have been reported[22] for the treatment of the salts of simple nitroalkanes with alkyl halides, and clearly involve initial attack of the alkylating agent at an oxygen atom of the nitro group. The exceptional behavior of gramine methiodide may indicate that the more rapid alkylation at oxygen (eq. 12) is reversible in this case, involving as it probably does[23] a conjugate addition to the enimine III. The irreversible C-alkylation is then



(12)

able to compete effectively. A similar argument has been advanced[24] to account for the competing C- and N-alkylation of enamines.

Discussion

Influence of Metal Ions.—The effect of magnesium ions in retarding the decarboxylation of nitroacetate *monoanion* is detectable in methanol solution (Table II) as in aqueous solution.[6] Much more striking is the stability of the *dianion* in methanol in the presence of magnesium ions. Under conditions where sodium methoxide is unreactive toward the monoanion, mag-

(18) The influence of carbon dioxide pressure has been more quantitatively defined by more recent experiments. The carboxylation of nitromethane at equilibrium (33°, 20 equivalents of MMC, DMF solution) reaches a sharp maximum at a carbon dioxide/magnesium ratio of 1.0, and falls to 75% of the maximum value at ratios of 0.8 and 1.3 (unpublished experiments by Dr. M. D. Buckmaster).

(19) The discrepancy between the yield of free acid isolated and that of the salt, determined spectrometrically, is to be expected, in view of the rapid decarboxylation of the acid in a moist environment. Feuer, Hass and Warren[20] reported isolation of 60–70% free acid upon hydrolysis of pure dipotassium nitroacetate.

(20) H. Feuer, H. B. Hass and K. Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).

(21) M. Stiles, *ibid.*, **81**, 2598 (1959).

(22) H. B. Hass and M. L. Bender, *ibid.*, **71**, 3482 (1949), and papers cited therein.

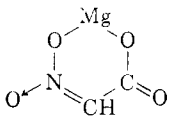
(23) J. D. Albright and H. R. Snyder, *ibid.*, **81**, 2239 (1959).

(24) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128 (1956).

nesium methoxide reacts with it, mole for mole, to form the stable divalent salt (see Fig. 1). Since $MgOCH_3^+$ is ordinarily a weaker base than sodium methoxide (compare, for example, their reactions with carbon dioxide), one must attribute this difference to a more favorable equilibrium in 14 than 13. The great influence of the metal ion in determining the position of this equilibrium indicates strong interaction between cation and anion in the divalent salt, and is most simply accounted for by the chelate structure II.

$$Na^+ + O_2NCHCO_2^- \rightleftharpoons NaO_2NCHCO_2^- \quad (13)$$

$$Mg^{++} + O_2NCHCO_2^- \rightleftharpoons MgO_2NCHCO_2 \quad (14)$$



II

The ultraviolet spectrum of II in methanol (λ_{max} 272, ϵ 11,300) is closely similar to that of the disodium salt in water (λ_{max} 274, ϵ 11,000). This similarity indicates that the electronic structure of the nitroacetate dianion is little influenced by the nature of the associated metal ion. The greater equilibrium constant for 14 compared to 13 must therefore arise not from differences in metal–ligand binding energy, but from entropy or solvation energy differences. Previous investigators[25] have indeed shown that the "chelate effect," when applied to metal ions such as zinc and cadmium which form outer orbital complexes, is accounted for by entropy rather than enthalpy terms. Such would be expected to be the case for magnesium complexes also.

Neither nitroacetic acid nor its sodium, potassium or diethylammonium salts is stable under the conditions where nitromethane is carboxylated by magnesium methyl carbonate. The success of this carboxylation reaction clearly rests, therefore, upon the influence of magnesium (or aluminum) ions upon the equilibrium of eq. 1. It is not clear at present whether there is also a catalytic effect of the coördinating metal ions in the carboxylation of nitroparaffins, as there apparently is in the carboxylation of ketones.[1] This question is currently being investigated.

Influence of Solvent.—The rate constant for the decarboxylation of nitroacetate monoanion is much greater in methanol than in water, and greater still in ether (Table II). Pedersen deduced[7] that, of the three tautomeric forms for the monoanion (IVa–c), the form IVa is the reactive one. In principle, the distribution of tautomers IVa–c could change appreciably as the solvent is varied, and rate differences might arise from this source. However, IVa is the major tautomer in all of the solvents studied, and thus the rate variation is far too great to be attributed to this cause.

$O_2NCH_2CO_2^-$ (IVa) $\quad$ $^-O_2N{=}CHCO_2H$ (IVb) $\quad$ $HO_2N{=}CHCO_2^-$ (IVc)

The solvent effect can be readily understood by comparing the polarity of the nitroacetate monoanion V with that of the transition state VI for its decarboxylation. The reaction is accompanied by a net movement of negative charge from the carboxylate group toward the dipolar nitro function, and the electrostatic energy liberated should be inveresely proportional to the dielectric constant of the medium.

$$^-O_2N^+{-}CH_2{-}CO_2 \longrightarrow [^{-\delta}O_2N{\cdots}CH_2{\cdots}CO_2^{-\delta}] \longrightarrow {}^-O\,N{=}CH_2 + CO_2$$

V VI

Experimental

Nitroacetic acid used in the decarboxylation studies was prepared as described by Steinkopf,[26] except that conversion of the dipotassium salt to the free acid was accomplished by adding an ice-cold aqueous solution of the salt to a rapidly stirred mixture of ether and concentrated hydrochloric acid (20% excess) at −5°, yields, 20–36%, m.p. 91–92° (reported[6a] 91.5–92.0°).

Ultraviolet spectral measurements were carried out using a Cary Model 11 spectrophotometer. The spectrum of undissociated nitroacetic acid (λ_{max} 274, ϵ 29.8) was observed in 4 *M* aqueous hydrochloric acid. The spectrum of the dianion (λ_{max} 275, ϵ 11,000) was taken in 0.12 *M* NaOH. The approximate absorption curve of the monoanion was constructed by carrying out a series of determinations of the decrease in absorption with time, of freshly prepared aqueous solutions of nitroacetic acid in water in the concentration range 10^{-3} *M* where it is almost completely dissociated. The experiment was repeated at 5 mμ intervals between 235 and 310 mμ and each curve was extrapolated to "zero time" to obtain the extinction coefficient. The broad maximum at 270–280 mμ had an extinction coefficient of approximately 210.

Determination of Acid Dissociation Constants.—Pure nitroacetic acid was dissolved in the appropriate volume of water, timing was begun, and the solution was transferred quickly to the spectrophotometer cell. The first reading was made 1 minute after dissolving the sample, the whole operation being carried out in a thermostated room at 23.5°. The decompositions under these conditions were cleanly first order for the first 10 minutes, so that extrapolation of the absorbance to zero time was easily done. Because the extinction coefficient of the monoanion was not known accurately, the folllowing procedure was used to calculate the concentration dissociation constant, K_1, from absorption data obtained in three such experiments.

$$K_1 = \frac{[H^+][HA^-]}{[H_2A]} = \frac{X_1^2}{C_1 - X_1} = \frac{X_2^2}{C_2 - X_2} = \frac{X_3^2}{C_3 - X_3} \quad (15)$$

Since the dianion concentration was negligible in these three solutions, the absorbance (A_1) of solution number 1, for example, was

$$A_1 = \epsilon(C_1 - X_1) + \epsilon' X_1 \quad (16)$$

where C_1 is the total concentration in solution 1, X_1 is the monoanion concentration in solution 1, and ϵ and ϵ' are the extinction coefficients for the free acid and the monoanion, respectively. From 16 and the analogous equation for solution number 2, ϵ' could be eliminated to give

$$X_2 = X_1(A_2 - C_2\epsilon)/(A_1 - C_1) \quad (17)$$

Combination of 17 and 15 allows calculation of X_1, and in similar fashion, X_2 and X_3. From three solutions where $C_1 = 16.0 \times 10^{-3}$, $C_2 = 8.00 \times 10^{-3}$ and $C_3 = 4.00 \times 10^{-3}$, the measured absorbances at 260 mμ (where ϵ 25.0) were 2.10, 1.18 and 0.64. The resulting values for K_1 are 0.0233, 0.0234 and 0.0234.

Determination of K_2 was carried out in borate buffer at only one *p*H, 8.80, where the contribution of the monoanion (ϵ_{260} *ca.* 200) to the absorption was very small compared to the dianion (ϵ_{260} 8,250), and where the uncertainty in its extinction coefficient had little effect on the final result. The absorbances of the solutions were obtained by the extrapolation method described above. From three solutions at *p*H 8.80 where the total nitroacetate concentrations were 6.20×10^{-4}, 4.60×10^{-4} and 1.55×10^{-4} the fraction dianion/monoanion was found to average 0.802. The corresponding value for K_2 is 1.25×10^{-9}.

Measurement of Decarboxylation Rates.—The rates of decarboxylation of nitroacetic acid in pH 8.80 sodium borate buffer were measured by following the decrease in absorption at 260 mμ as described in the preceding section. The reaction was cleanly first order and the observed first-order rate constant, obtained by plotting log *A vs.* time, was related to the rate constant, *k*, for decomposition of the monoanion by eq. 2.

The decarboxylation rates of the monoanion in methanol and ether were measured by following the change in absorption at 275 mμ of solutions prepared by mixing freshly prepared solutions of the acid and base in the appropriate solvent. The first-order rate constant was obtained from t_b, the time elapsed before the "break" in the absorption curve (see Fig. 1), by use of eq. 6. Table IV gives the data obtained in this way.

Aluminum nitroacetate was precipitated as a white amorphous powder when ether solutions of nitroacetic acid and aluminum isopropoxide were mixed. The samples from two experiments in which the mole ratio of alkoxide to acid was 1.4 (sample 1) and 0.5 (sample 2) were dried *in vacuo* over P_2O_5 and analyzed. Aluminum analysis by the 8-hydroxyquinoline method[27] indicated 11.1% Al in sample 1 and 10.6% in sample 2. Taken with

(25) C. G. Spike and R. W. Parry, *J. Am. Chem. Soc.*, **75**, 2726, 3770 (1953); see F. J. C. Rossotti, in "Modern Coordination Chemistry," edited by J. Lewis and R. G. Wilkins, Interscience Publishers, Inc., New York, N. Y., 1960, p. 58.

(26) W. Steinkopf, *Ber.*, **42**, 3925 (1909).

(27) S. E. Wiberley and L. G. Bassett, *Anal. Chem.*, **21**, 609 (1949).

TABLE IV

KINETIC DATA FOR DECARBOXYLATION OF NITROACETATE MONOANION IN METHANOL

Salt	$10^3 n_A$	$10^4 n_B$	t_b	k, min.$^{-1}$
Magnesium	4.66	1.50	5.0	0.421
	7.50	1.50	9.5	.421
	9.32	1.50	11.5	.452
	12.43	1.50	17.5	.416
	7.50	0.75	20.5	.440
	7.50	2.25	5.8	.401
	7.50	3.00	3.8	.394
	7.50	3.75	2.3	.434
			Average	0.42
Sodium	16.0	8.0	1.7	0.59
	16.0	4.0	4.7	.63
	16.0	8.2	1.7	.57
			Average	0.60
Dimethyl-ammonium	16.0	8.0	1.6	.63
	16.0	8.3	1.5	.62
	16.0	4.0	4.4	0.68
	8.5	4.2	1.8	.57
			Average	0.63

the combustion analysis, these figures indicate a nitrogen to aluminum ratio of 1.43 and 1.42, respectively, in the two samples.

Anal. Found[28] (sample 1): C, 33.5; H, 6.0; N, 8.2; (sample 2): C, 29.5; H, 4.6; N, 7.7.

The most likely formula seems to be $Al_2(O_2NCHCO_2)_3 \times 2$ solvent, where the solvent is either isopropyl alcohol or ether. Calcd. for $C_{14}H_{23}O_{14}N_3Al_2$: C, 32.9; H, 4.5; N, 8.2; Al, 10.6. For $C_{12}H_{19}O_{14}N_3Al_2$: C, 29.8; H, 4.0; N, 8.7; Al, 11.2.

The aluminum salt was slowly decomposed in pure water, presumably because of slight hydrolysis to the monoanion. Hydrolysis in strong acid led to the recovery of free nitroacetic acid, identified by melting point and infrared spectrum.

Carboxylation of Nitromethane (Methanol Solution).—A solution of MMC in methanol was prepared by dissolving 12.0 g. (0.50 g.-atom) of magnesium in 250 ml. of dry methanol and stirring the resulting slurry of the methoxide under carbon dioxide (Matheson bone dry carbon dioxide was used throughout this work) for 19 hours. Considerable heat was evolved early in the reaction, but after the time stated, no heat was detected and the solution was clear, pale yellow-orange. Portions of this solution were mixed with varying amounts of nitromethane at 18°, 30° and 40°, and the ultraviolet absorption was observed on aliquots, appropriately diluted with methanol. The development of a peak at 272 mμ was observed to occur over a period of hours. The rate of the spectral change was increased by an increase in either MMC or nitromethane concentration, and was about 17 times as fast at 40° as at 18°. The highest conversion observed was 2.5% of the theoretical yield based on nitromethane; work-up of this solution as described in the following experiment produced 0.5% yield of crystalline nitroacetic acid, identified by melting point and infrared spectrum.

Carboxylation of Nitroparaffins (Dimethylformamide Solution).—A stock solution of magnesium methyl carbonate (MMC) in dimethylformamide (DMF) was prepared as follows. Over a period of 16 hr., 480 g. (20 g.-atoms) of magnesium turnings was added to 8 l. of dry methanol in a 12-l. flask equipped with condenser, stirrer and gas inlet tube. After the magnesium had reacted completely, methanol was removed under reduced pressure at a bath temperature of 50°. Dimethylformamide (commercial untreated) was added to give a total volume of 10 l. and carbon dioxide was added to the stirred solution as rapidly as it was absorbed. After the solid had dissolved, a Claisen head was attached to the flask and residual methanol was distilled under a slow stream of carbon dioxide until the temperature of the head reached 110°. Then a 5-plate bubble-cap column was attached and distillation continued until the head temperature reached 152°. The solution was then cooled to room temperature and stirred under carbon dioxide for 1–3 hours, when saturation appeared complete.

(a) **Nitroacetic Acid.**—Three grams (0.049 mole) of nitromethane was added to 100 ml. of 1.94 *M* MMC solution at 50°, and the solution was stirred at this temperature for 2 hr. while passing a slow stream of nitrogen through the reaction mixture. A 1-ml. aliquot diluted 2500-fold with methanol exhibited the absorption maximum at 272 mμ corresponding to complete conversion to magnesium nitroacetate. The cooled (10°) solution was then poured into a mixture of 80 ml. of concentrated hydrochloric acid and 100 g. of ice layered over with 100 ml. of ether. The ether layer was separated, the aqueous solution was extracted further with five 50-ml. portions of ether, and the extracts were dried briefly over magnesium sulfate, then over phosphorus pentoxide. Removal of ether left a residue which crystallized upon the addition of a few ml. of chloroform. The product (3.3 g., 63%) melted at 89–92° without further purification and was identical with material prepared as described in an earlier paragraph. When the reaction was carried out with only 1.0, 1.5 or 2.0 equivalents of MMC per mole of nitromethane, the yield of magnesium nitroacetate was 35, 52 and 67%, respectively, as determined spectroscopically. The yield was also decreased by more than a factor of two when the sweep gas was carbon dioxide instead of nitrogen.

(b) **α-Nitropropionic acid** was prepared in 49% yield from nitroethane and MMC, using the same procedure. The product melted at 59–61° (reported[29] 61.0–61.5°) after recrystallization from chloroform–carbon disulfide.

(c) **Methyl 2-Nitro-4-methylpentanoate.**—1-Nitro-3-methylbutane[30] (10.5 g., 0.090 mole) was treated with 250 ml. of 2 *M* MMC solution at 50–55° as described under (a). After 1.5 hr. a 1-ml. aliquot diluted 2500-fold with methanol exhibited a maximum at 268 mμ (*A* 0.50); after 5.5 hr. the absorbance had increased to 1.05; after 7.1 hr. it was 1.00. The mixture was then cooled and added slowly at Dry Ice temperature to 500 ml. of dry methanol saturated with hydrogen chloride. The methanol solution was allowed to warm to room temperature while stirring overnight and for an additional 8 hr. The methanol solution was then evaporated at the water-pump to about one-half its original volume and extracted twice with ether. The DMF–salt layer was then added to an equal volume of cold water and again extracted twice with ether. The combined ether solution was washed three times with water and dried over magnesium sulfate. Distillation yielded 7.20 g. (46%) of colorless nitro ester, b.p. 57–60° (3 mm.), $n^{25}D$ 1.4288 ν_{CO} 1760 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 48.03; H, 7.44; N, 8.02.

The nitro ester (5.00 g., 0.0286 mole) was hydrogenated at room temperature in 100 ml. of methanol with 0.2 g. of PtO_2 at 45 p.s.i.g. The crude amino ester was refluxed with distilled water for 3 hr., treated with charcoal, filtered, and concentrated to produce, in several crops, 3.38 g. (90%) of DL-leucine, m.p. 293–294° dec. (sealed tube) (reported[31] 293–295°), identified by comparison of the infrared spectrum with a commercial sample.

The amino acids listed in Table III were prepared by carboxylating the appropriate nitroalkane as described under (a). The crude nitro acid was dissolved in 50–70 ml. of acetic acid and hydrogenated at 50 p.s.i.g. using 1.0 g. of 10% palladium-on-carbon catalyst. Complete hydrogenation usually required about 18 hr. at room temperature. After filtration of the catalyst, acetic acid was removed under reduced pressure at 70° until the volume was approximately 10 ml. Ether was then added to precipitate the amino acid which was recrystallized from ethanol. In each case the amino acid was characterized by comparison of its infrared spectrum with that of a commercial sample; DL-alanine (46%), m.p. 292–294° dec.; DL-α-aminobutyric acid (34%), m.p. 283–285° dec.; DL-norvaline (42%) m.p. 290–292° dec.

3-(2-Nitroethyl)-indole.—The reaction between 6.1 g. (0.10 mole) of nitromethane and 100 ml. of 1.94 *M* MMC solution was allowed to proceed for 1 hour as described under (a). Gramine methiodide (2.0 g., 0.0063 mole) was then added and the reaction mixture was stirred at 50° for 20 hr. under a nitrogen atmosphere. The solution was then poured into 200 ml. of *p*H 5 aqueous acetate buffer and stirred for 2 hr. at room temperature to complete the decarboxylation. The solution was extracted with ether, dried over magnesium sulfate, and evaporated to an oil. The oil was dissolved in methanol and treated with charcoal, and water was added to the cloud point. The yield of product was 1.18 g. (98.5%), m.p. 52–55° (reported[32] m.p. 55.5–56.0°) identical with the sample prepared as described previously.[32]

Attempted Alkylation with Benzyl Bromide.—A solution of magnesium nitroacetate in methanol, prepared from 5.25 g. (0.050 mole) of nitroacetic acid and 100 ml. of 050 *M* magnesium methoxide, was treated with 8.5 g. (0.05 mole) of benzyl bromide at 50° for 2 hr. The usual acid work-up yielded 4.2 g. of a pale oil whose infrared spectrum lacked the characteristic 1560 cm.$^{-1}$ band of aromatic nitro compounds, but exhibited 1700 cm.$^{-1}$ carbonyl absorption, characteristic of benzaldehyde. Treatment with Brady reagent yielded the DNP of benzaldehyde, m.p. and mixed m.p. 236–237°.

Solubility of Carbon Dioxide in Methanolic Magnesium Methoxide.—Fifty milliliters of a methanol solution containing 0.035 mole of magnesium methoxide was placed in a thermostated flask (30°) attached to a vacuum line containing a large

(28) Spang Microanalytical Laboratory, Ann Arbor, Mich.

(29) W. Steinkopf and A. Supan, *Ber.*, **43**, 3239 (1910).

(30) N. Kornblum, B. Taub and H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954).

(31) E. Fischer, *Ber.*, **33**, 2373 (1900).

(32) D. A. Lyttle and D. I. Weisblatt, *J. Am. Chem. Soc.*, **77**, 5747 (1955).

mercury-filled gas storage buret and two manometers, for measuring pressure in both the buret and the equilibration flask. The free volume in the flask and line were known. Increments of carbon dioxide were admitted to the flask and the solution was stirred magnetically until equilibrium was reached. Measurement of total pressure over the solution allowed calculation of the quantity of carbon dioxide absorbed by the solution after each addition. Figure 2 is a plot of the data.

Repetition of the experiment with pure methanol (measured vapor pressure at 30°, 162 mm.; literature,[33] 163 mm.) yielded the following solubility data, in mmoles of carbon dioxide per 50 ml. of methanol at the indicated pressure: 1.6 at 566 mm., 2.7 at 621; 3.2 at 688, 3.5 at 723.

(33) N. A. Lange, "Handbook of Chemistry," 9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1956, p. 1432.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO, LONDON, ONTARIO, CANADA]

Toxic Fluorine Compounds. XVIII.[1] The Synthesis of the Toxic Principle of *Dichapetalum toxicarium* (18-Fluoro-*cis*-9-octadecenoic Acid) and Related ω-Fluoro Unsaturated Acids[2,3]

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18-Fluoro-*cis*-9-octadecenoic acid (ω-fluoro-oleic acid), synthesized in 36.5% over-all yield utilizing acetylenic intermediates, has been shown to be identical with the toxic principle of *Dichapetalum toxicarium*. Other ω-fluoro unsaturated acids have been prepared, including the isomeric *trans*-acid (ω-fluoro-elaidic acid). The toxicities of all new ω-fluoro compounds have been determined; the results, interpreted in terms of previously reported metabolic routes, provide additional evidence for the catabolism of aliphatic halides, nitriles and acids.

Dichapetalum toxicarium (*Chailletia toxicaria*, Don), a glabrous shrub occurring in Sierra Leone, produces a hard and woody fruit which is extremely toxic to warm-blooded animals. The powdered fruit has been used for killing rats; the common name of "ratsbane" has therefore been coined for the shrub. It is also known as "broke back" from its effect in producing paralysis of the lower limbs. The pharmacological, medical and historical aspects of the plant have recently been reviewed.[4] It has been widely used locally as an arrow poison, for poisoning enemy water supplies and, by witch doctors, for terrorizing the native population.

Peters and colleagues have concluded,[5] on the basis of nuclear magnetic resonance, infrared spectroscopy and ozonolysis, that the toxic principle is ω-fluoro-oleic acid. It was in order to confirm this conclusion that the following synthesis was undertaken, starting from 8-fluoro-octyl bromide

$$F(CH_2)_8Br + NaC{\equiv}CH \longrightarrow F(CH_2)_8C{\equiv}CH + I(CH_2)_7Cl \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7Cl + NaCN \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7CN \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7CONH_2 \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7COOH \longrightarrow$$
$$F(CH_2)_8CH{=}CH(CH_2)_7COOH(cis)$$

Because 8-fluoro-octyl bromide[6] is expensive and time-consuming to prepare, the entire synthesis was first carried out on a trial basis starting from the more readily available 6-fluorohexyl bromide.[6] This led to 16-fluoro-*cis*-9-hexadecenoic acid (ω-fluoropalmitoleic acid), an interesting compound in its own right and one which provided a ready source of 16-fluorohexadecanoic acid (ω-fluoropalmitic acid). The toxicities of these acids are discussed later.

8-Fluoro-octyl bromide, previously prepared[6] in low yield from 1,8-dibromo-octane by partial halogen exchange, was obtained in 89% yield from 8-fluoro-octanol[7] by treatment with phosphorus tribromide. Conversion of the fluorobromide to 10-fluoro-1-decyne was accomplished in 60% yield by reaction with sodium acetylide in xylene–dimethylformamide[8]; the use of organic solvents for the preparation of sodium acetylide and for its subsequent reaction with ω-fluoroalkyl halides is more convenient than the older procedure[9] involving liquid ammonia. An even more convenient procedure involves the very recently introduced[10] lithium acetylide stabilized as the ethylenediamine complex; use of this material obviates the need for gaseous acetylene and gives a higher yield of product. Thus, 6-fluorohexyl chloride gave 8-fluoro-1-octyne in 71% yield. This is the only method which gives high yields of 1-alkynes directly from chlorides; however, the use of bromides is usually preferable because of a lower reaction temperature, and because the chlorides and resultant 1-alkynes have very similar boiling points.

Previous work[9] had indicated that the ω-fluoro-1-alkynes, in the presence of reactants such as sodamide and Grignard reagents, tended to give fluorine-free mixtures rather than form the expected ω-fluoroacetylides. In initial attempts to convert 10-fluoro-1-decyne to 1-chloro-17-fluoro-8-heptadecyne, preformed lithium amide in liquid ammonia was examined as the reagent; no reaction occurred, and unchanged starting materials were recovered. However, by using lithium amide formed *in situ*[11] from pure metallic lithium in liquid ammonia, 10-fluoro-1-decyne and 1-chloro-7-iodoheptane gave the required chlorofluoroheptadecyne in 89.4% yield. Reaction of this last compound with sodium cyanide in dimethyl sulfoxide[12] produced the corresponding nitrile in 93.5% yield.

Preliminary work using 15-cyano-1-fluoro-7-pentadecyne had indicated the difficulty of hydrolyzing this type of nitrile, because the triple bond is susceptible to strongly acidic reagents and the fluorine to vigorous alkaline treatment. Methanolysis was therefore examined, using absolute methanol saturated with hydrogen chloride; but, in the course of the reaction, the triple bond was also affected, forming methyl 9(10)-chloro-16-fluoro-9-hexadecenoate, $F(CH_2)_6CH{=}CCl(CH_2)_7COOCH_3$ (or the 10-isomer). Subsequent attempts at methanolysis using methanol and concentrated sulfuric acid resulted in concomitant hydration of the triple bond, giving methyl 16-fluoro-9(10)-oxohexadecanoate. The desired 16-fluoro-9-hexade-

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(9) F. L. M. Pattison and J. J. Norman, *J. Am. Chem. Soc.*, **79**, 2311 (1957).

(10) Foote Mineral Co., Route 100, Exton, Pa.

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