FLUORINATED AMINO ACID DERIVATIVES

by

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INTRODUCTION

The physiological effects of aliphatic organic compounds containing fluorine have been reviewed in detail by Saunders[1,2] and Pattison[3] and it is generally accepted that the toxic action of many aliphatic fluoro organic compounds is due to their ability to be converted by β-oxidation to fluoroacetic acid. Once formed, the fluoroacetic acid is metabolized in the Krebs tricarboxylic acid cycle to fluorocitric acid which deactivates aconitase, blocks the cycle and causes accumulation of citric acid in various tissues.[4]

The toxic members in most homologous series are those which contain an even number of carbon atoms, since β-oxidation leads to the formation of fluoroacetic acid. Those compounds which contain an odd number of carbon atoms are generally non-toxic.

In w-monofluoro-α-amino acids, Raasch[5] observed that the toxic members were those with an odd number of carbon atoms. Toxicity determinations on white swiss mice by intraperitoneal injection indicated that 5-fluoronorvaline was very toxic (LD_{50}=1.08 mg/kg) whereas 6-fluoronorleucine was non-toxic (LD_{50}=215 mg/kg).

A degradative mechanism involving oxidative deamination, oxidative decarboxylation and finally β-oxidation leading to fluoroacetic acid was postulated to support these observations:

$F(CH_2)_3CH(NH_2)CO_2H$ $F(CH_2)_3COCO_2H$ $F(CH_2)_3CO_2H$ FCH_2CO_2H.

Our goal was to prepare 2-amino-4-fluoro-3-methylpentanoic acid (1)

$CH_3CHFCH(CH_3)CH(NH_2)COOH$

1

which is a branched amino acid with no terminal fluorine atoms and therefore expected to be non-toxic.

HISTORICAL

The discovery of the highly toxic nature of fluoroacetic acid stimulated the investigation of many aliphatic fluoro compounds[6] during World War II.

Yet prior to the 1950s, research in the field of fluorine-containing amino acids was confined to the synthesis and testing of the aromatic series. Since some of these fluoro-aromatic analogs proved to have effective antimetabolic properties, it seemed only a matter of time before attention would turn towards the investigation of the fluoro derivatives of the aliphatic series.

The preparation of aliphatic fluoro amino acids was first reported in a patent[7] in 1953; since then, many examples employing various synthetic approaches have been recorded. Although the primary objective of the efforts in this field has been directed towards biological applications, much of the chemistry which has evolved is in itself quite interesting.

The first synthesis of aliphatic amino acids containing a single substituent was reported by Lontz and Raasch[5,7]. The reaction of w-fluoro alkyl bromides with the sodio derivative of diethyl acetamidomalonate proceeded readily to form the diethyl acetamido(w-fluoroalkyl) malonate intermediate (I):

$$F(CH_2)_nBr + Na\text{-}\underset{\underset{NHAC}{|}}{CH}(CO_2Et)_2 \qquad F(CH_2)_n\text{-}\underset{\underset{NHAC}{|}}{C}(CO_2Et)_2$$

I

where n=3,4

Hydrolysis with hydrofluoric acid of (I) gave 5-fluoronorvaline (II) and 6-fluoronorleucine (III) in 27 and 55 per cent yields, respectively:

$FCH_2CH_2CH_2CH(NH_2)COOH$ — II

$FCH_2CH_2CH_2CH_2CH(NH_2)COOH$ — III

Attempts to prepare the corresponding 2-amino-4-fluoro butyric acid using 1-bromo-2-fluoroethane in the initial condensation step resulted in a low yield of the intermediate (I with n=2) which, on hydrolysis, lost most of the fluorine, and the corresponding hydroxy compound (IV)

$HOCH_2CH_2CH(NH_2)COOH$

was obtained.

The isolation of α-fluoro-β-alanine as a metabolic product of 5-fluoro uracil[8] prompted Bergmann and Cohen[9] to undertake the synthesis of this compound.

Diethyl fluoromalonate was condensed with formaldehyde and gave diethyl α-fluoro-α-hydroxymethyl malonate:

$$FCH(CO_2Et)_2 + HCHO \xrightarrow[HCO_2H]{\text{Piperidine}} HOCH_2CF(CO_2Et)_2$$

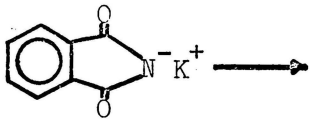
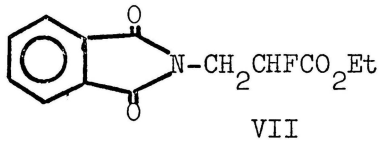
IV

Alkaline cleavage of the ester IV gave the expected α-fluoro-β-hydroxy propionate (V) which was converted, without isolation, into its methanesulfonate (VI):

$$HOCH_2CHFCO_2Et \xrightarrow{CH_3SO_2Cl} CH_3SO_3CH_2CHFCO_2Et$$

V VI

The sulfonate group in (VI) was displaced with potassiophthalimide and hydrolysis of the intermediate phthalimdo compound (VII) with hydrochloric acid resulted in a 41 per cent yield of the hydrocholoride of the desired amino acid (VIII)

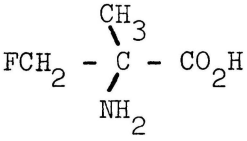
VI +  → 

VII

VII + HCl ⟶ $H_2NCH_2CHFCOOH$

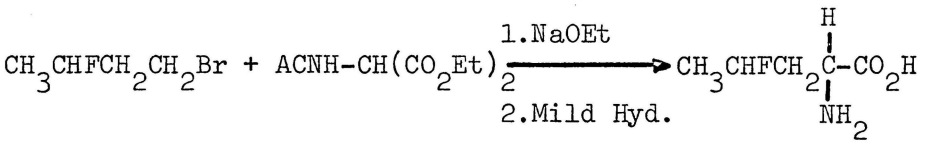
VIII

Christensen and Oxender[10] prepared 2-methyl-3-fluoro alanine (IX), wuing a modification of the Strecker synthesis. By treating an aqueous solution of monofluoroacetone with a mixture of potassium cyanide and ammonium chloride and subsequently hydrolyzing the mixture with hydrochloric acid, a 64 per cent yield of the amino acid (IX) was obtained.



IX

From the alkylation of the sodium salt of diethyl acetamidomalonate with 1-bromo-3-fluorobutane, followed by mild hydrolysis with dilute hydrochloric-acetic acid mixture, Hudlicky et al.[11] obtained 5-fluoronorleucine (X)



X

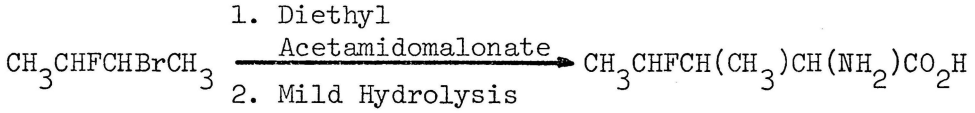
Attempts to replace the tosyl group by fluorine in the tosyl derivatives of ethyl 2-ethoxycarbonyl-2-acetamido-3-methyl-5-hydroxyvalerate (XI) were unsuccessful.[7]

DISCUSSION OF RESULTS

Project 1

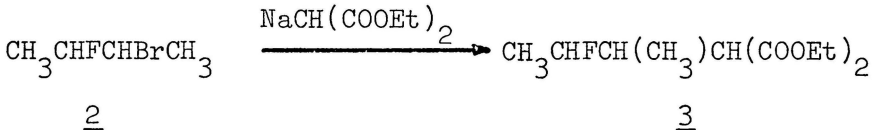
One of the first attempts to synthesize 4-fluoroisoleucine (1) was to follow the procedure developed by Hudlicky et al.[11].

From the alkylation product of the sodium salt of ethyl acetamidomalonate and 2-bromo-3-fluorobutane (2), followed by mild hydrolysis with a mixture of dilute hydrochloric and acetic acid we should obtain the desired amino acid:

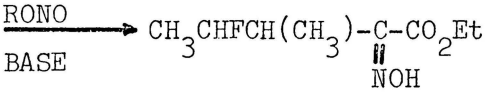


$CH_3CHFCHBrCH_3$ (2) → $CH_3CHFCH(CH_3)CH(NH_2)CO_2H$ (1)

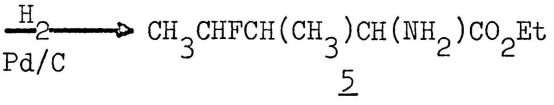
Another option was to alkylate the sodium salt of ethyl malonate with 2, then to treat the resulting ethyl 4-fluoro-3-methyl-2-ethoxycarbonylpentanoate (3) with alkyl nitrite under basic conditions and then to reduce the hydroxylamino intermediate (4):



$CH_3CHFCHBrCH_3$ (2) → $CH_3CHFCH(CH_3)CH(COOEt)_2$ (3)



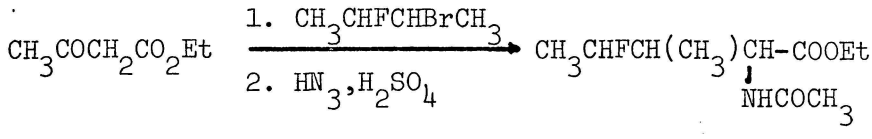
$CH_3CHFCH(CH_3)-C(=NOH)-CO_2Et$ (4)



$CH_3CHFCH(CH_3)CH(NH_2)CO_2Et$ (5)

The hydrolysis of aminoester (5) would then give 1. In the event that basic conditions should cause elimination of fluorine we still have another option.

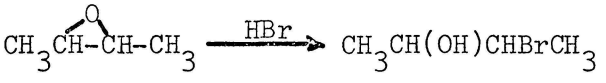
The alkylation product of the sodium salt of ethyl acetoacetate and 2-bromo-3-fluorobutane (2) should undergo Schmidt reaction under acidic conditions to give ethyl 4-fluoro-2-N-acetylisoleucine (6)



6

which could be hydrolyzed to 1 under mild acidic conditions.

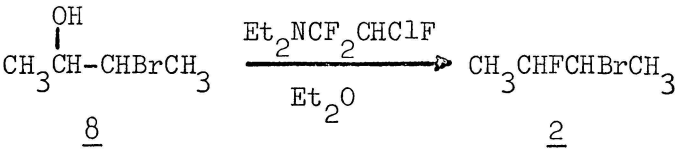
We first tried to develop a method for the preparation of 2-bromo-3-fluorobutane (2). The method selected started with the treatment of 2,3-epoxybutane (7), which is commercially available, with 48 per cent hydrobromic acid which gave 3-bromo-2-butanol (8):



7 8

as previously reported by Winstein and Lucas.[12]

The next step was the introduction of fluorine by means of 2-chloro-1,1,2-trifluorotriethylamine[13] (9):



8 2

We indeed prepared 2 by the method shown above but since 2,3-epoxybutane is very expensive, we devised another route to 2-bromo-3-fluorobutane (2) which for the present moment is the most convenient synthetic method for the preparation of 2.

Bromination of methyl ethyl ketone gave 3-bromo-2-butanone (10) in 75 per cent yield,[14] and lithium aluminum hydride reduction of 10 gave 3-bromo-2-butanol in 56 per cent yield.

$$CH_3COCH_2CH_3 + Br_2 \xrightarrow[H_2O]{KClO_3} CH_3COCHBrCH_3 \xrightarrow[Et_2O]{LAH} CH_3CHOHCHBrCH_3$$

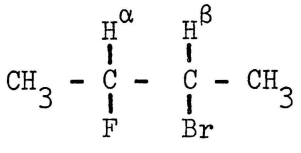
10 8

Conversion of 8 to 2-bromo-3-fluorobutane was achieved by using 2-chloro-1,1,2-trifluorotriethylamine as mentioned before.

All attempts to perform a C-alkylation with 2-bromo-3-fluorobutane and any of the active methylene compounds failed (see Appendix, Table I).

The results can be summarized as follows: - if the temperature of the reaction is too low (up to 100°) and the reaction time relatively short (up to 4 hr) starting material is recovered.
- if the temperature is increased over 120° the fluorine is lost from the molecule.

A reasonable explanation for such inertness of 2-bromo-3-fluoro-butane toward alkylation is that the high electronegativity of fluorine makes the carbon-bromine bond very tight and the β-hydrogen



very labile since it is α-to bromine and β-to fluorine. Under those circumstances the elimination of hydrogen fluoride occurred more readily than the S_N2 displacement of the secondary bromine.

One way to overcome the problem of alkylation which was attempted was to introduce fluorine into the molecule later in the reaction sequence.

The alkylation product of 3-bromo-2-butanone (10) and the sodium salt of diethylmalonate could be reduced to ethyl 2-ethoxycarbonyl-4-hydroxy-3-methylpentanoate (12), and the hydroxyl group displaced by fluorine:

$$CH_3COCHBrCH_3 + CH_2(CO_2Et)_2 \xrightarrow{NaOEt} CH_2COCH(CH_3)CH(CO_2Et)_2$$

10 11

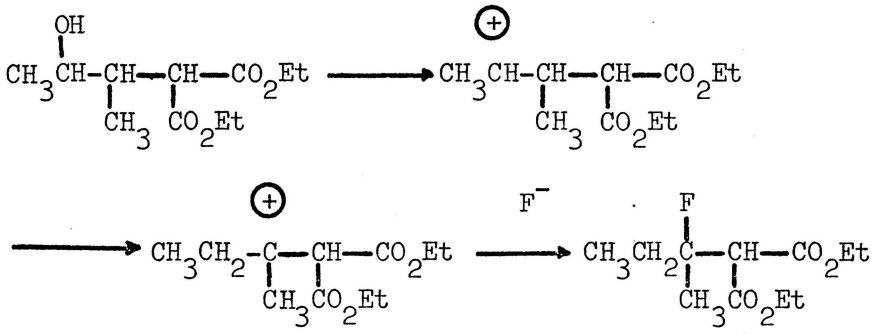
$$\xrightarrow{\text{Reduction}} CH_3CH(OH)CH(CH_3)CH(CO_2Et)_2$$

12

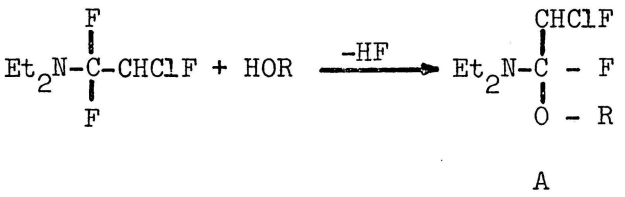
$$\xrightarrow[Et_2O]{Et_2NCF_2CHClF} CH_3CHFCH(CH_3)CH(CO_2Et)_2$$

3

The only question that arose at this time was whether the displacement of the hydroxyl group by fluorine using 2-chloro-1,1,2-trifluoro-triethylamine would not involve a free carbonium ion. If a free carbonium ion were formed during the conversion it would give a wring product due to the following rearrangement:

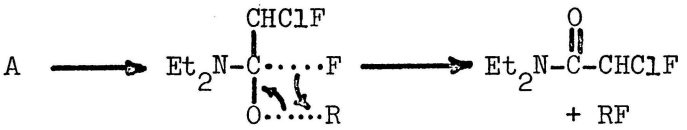


In order to test this possibility, we performed a model experiment using 2-methylpropanol to test which one of the two possible mechanisms is operating:

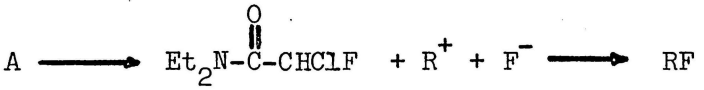


A

Mechanism A



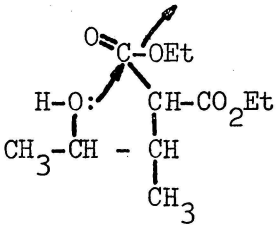
Mechanism B



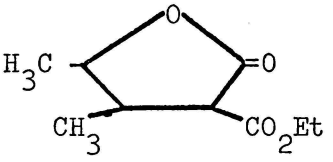
Since 2-methyl-1-propanol gave the non-rearranged product 2-methyl-1-fluoropropane, this result suggested that the mechanism is concerted.

Alkylation of the sodium salt of diethylmalonate with 3-bromo-2-butanone (10) proceeded as expected and ethyl 2-ethoxycarbonyl-4-keto-

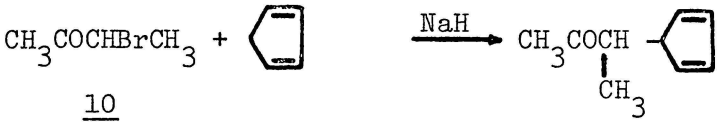
3-methylpentanoate (11) was obtained in 60 per cent yield. Unfortunately during the reduction of 11 a lactone was obtained instead of 12:



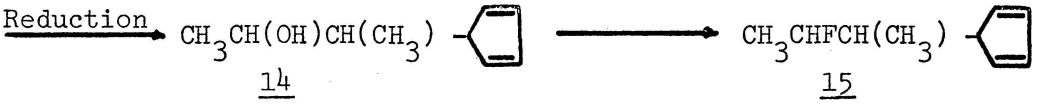
12



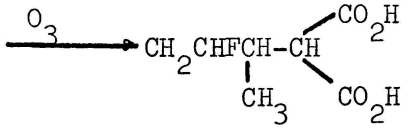
One more attempt to make ethyl 2-ethoxycarbonyl-4-fluoro-3-methyl-pentanoate (3) was made. Alkylation of the sodium salt of cyclopentadiene with 10 should give 5-(2'-keto-1'-methyl)propyl-1,3-cyclopentadiene (13) which could be easily reduced using an appropriate complex metal hydride so that the resulting alcohol could not lactonize. After the introduction of fluorine, the conjugated diene could be converted into a dicarboxylic acid by means of ozone:



10 13



14 15



16

Alkylation of cyclopentadiene with 10 appeared to occur satisfactorily as evidenced by the formation of sodium bromide in the expected amount. However, attempted distillation of the resulting product (13) failed since polymerization occurred, and this route was abandoned.

Summary

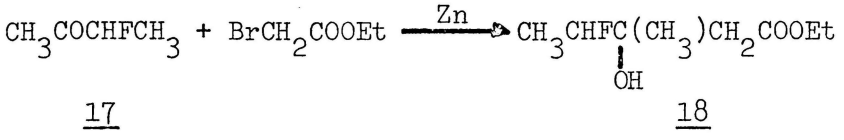
1. A new synthetic approach in the synthesis of 2-bromo-3-fluorobutane has been developed.
2. All attempts to alkylate the sodium salt of diethyl malonate, diethyl acetamidomalonate, or ethyl acetoacetate with 2-bromo-3-fluorobutane failed.
3. Attempts to prepare 2-carboxy-4-fluoro-3-methylpentanoic acid (or its ethyl ester) from 3-bromo-2-butanone and the sodium salt of cyclopentadiene or diethyl malonate also failed.

Project 2

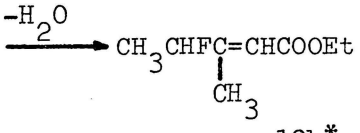
Owing to the fact that all attempts to use alkylation failed we tried to design another approach to link two carbon units together. One part must have fluorine in the desired position while the other must possess the carboxyl group and the precursor of an amino group in the α-position.

There are two reactions of choice; a Reformatsky reaction and a Wittig reaction.

At first we considered a Reformatsky reaction between 3-fluoro-2-butanone (17) and ethyl bromoacetate. Dehydration of ethyl 4-fluoro-3-hydroxy-3-methylpentanoate (18) should give ethyl 4-fluoro-3-methyl-2-pentenoate (19):



17 18



19b*

Reduction of 19 followed by hydrolysis should give 4-fluoro-3-methyl-pentanoic acid (21):

---

*Throughout the thesis, letters a,b,c, and d refer to methyl, ethyl, tert-butyl, and benzylesters, respectively.

$$19b + H_2/Rh\text{-}Al_2O_3 \longrightarrow CH_3CHFCH(CH_3)CH_2COOEt$$

20b

$$\xrightarrow{H^+} CH_3CHFCH(CH_3)CH_2COOH$$

21

Bromination of acid 21 under the conditions of the Hell-Volhard-Zelinsky reaction[15] followed by addition of the appropriate alcohol would give an ester of 2-bromo-4-fluoro-3-methylpentanoate (22):

$$CH_3CHFCH(CH_3)CH_2CO_2H \xrightarrow[2.\ ROH]{1.\ P,Br} CH_3CHFCH(CH_3)CHBrCOOR$$

21 22a-d

R=Me.....a
=Et.....b
=tert-Bu....c
=$PhCH_2$-.....d

Treatment of 22 with sodium azide followed by reduction would give an α-amino ester (24) which could be converted to the desired amino acid, 2-amino-4-fluoro-3-methylpentanoic acid:

$$CH_3\underset{F}{CH}\text{-}\underset{CH_3}{CH}\text{-}\underset{Br}{CH}\text{-}CO_2R \xrightarrow[MeOH,reflux]{NaN_3} CH_3CHFCH(CH_3)CH(N_3)COOR$$

23

$$\xrightarrow[Pd/C]{H_2} CH_3CHFCH(CH_3)CH(NH_2)COOR$$

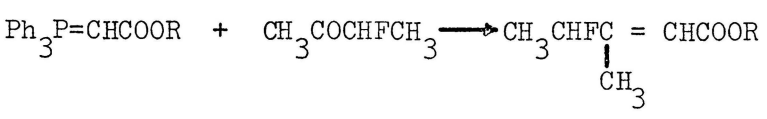
24

The advantage of the outlined approach is that fluoro ketones are relatively easy to prepare and, by simple variations in the fluorine

position, one could obtain different amino acids using the same sequence of reactions.

Upon checking the literature we found that Bergmann and co-workers[16] had difficulties during dehydration of the hydroxyester 18 to the unsaturated ester 19. Because of that we abandoned this plan.

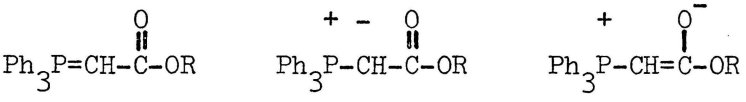
Another possibility was to use a Wittig reaction[17] which would give an ester of 4-fluoro-3-methyl-2-pentenoic acid (19) in one step:



19

We did perform that reaction but 19 was obtained in a very low yield and, furthermore, the experimental conditions had to be very vigorous (24 hr at 120°).

The reason for the above reaction being so slow is probably due to the double stabilization of the carbanion by phosphorus and by the carboxyl group:



To overcome this problem Horner[18] and Emmons[19] prepared phosphonates which are very reactive. They react with ketones exothermically even at room temperature. In addition, the phosphorus product is a phosphate ester and hence soluble in water which makes it easy to separate from the olefinic product.

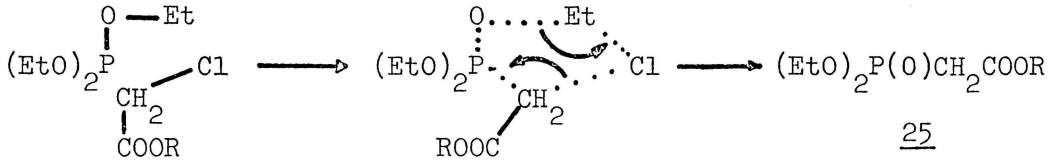
The phosphonates are also cheaper than triaryl phosphines and may

be easily prepared by the Arbuzov reaction:[20]

$$(EtO)_3P + Cl(Br)CH_2COOR \longrightarrow (EtO)_2P(O)CH_2COOR$$

25a-d

The mechanism of this reaction is suggested to proceed through a five-membered transition state:



25

The next step was to find the best procedure for the preparation of 3-fluoro-2-butanone (17).

Bergmann and his group prepared 17 from 3-chloro-2-butanone[21] and potassium fluoride in glyme:[22]

$$CH_3COCHClCH_3 + KF \xrightarrow[\text{glyme}]{180^\circ} CH_3COCHFCH_3$$

26 17

We successfully followed this method and found that the isomeric products of chlorination of 2-butanone are very difficult to separate due to the very close boiling points of 1-chloro-2-butanone, 3-chloro-2-butanone, 2-butanone and some polychlorinated 2-butanones.

Attempts to reproduce the method of Kosower et al.[23] for the preparation of 3-chloro-2-butanone (26) from 2-butanone, copper (II) chloride and lithium chloride in N,N-dimethylformamide (DMF) were not

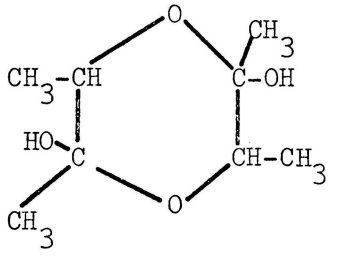
successful. We did obtain 26 but only in 15 per cent yield although the authors[23] claimed 70 per cent yield.

Another attempt has been made using acetoin (3-hydroxy-2-butanone) as a starting material for the preparation of 3-fluoro-2-butanone.

The reason for these attempts was that acetoin is commercially available and the hydroxy group should be easily displaced by fluorine.

Table II (See Appendix) shows reagents which we used but which were unsuccessful.

The explanation we have is that acetoin exists in a dimeric form which reduces the reactivity of the hydroxyl group toward displacements:



We can now summarize the problems involved in the preparation of 3-fluoro-2-butanone (17):

1. The Bergmann method[21,22] suffers from using 3-chloro-2-butanone as a starting material because of its tedious process of purification.
2. Yields described by Kosower[23] were not reproducible.
3. Acetoin is not a suitable starting material for the preparation of 17 because the hydroxyl group could not be displaced by fluorine.

An attempt was made to use 3-bromo-2-butanone as a starting

material. The original procedure describing bromination of 2-butanone[28] required six consecutive fractional distillations to purify 3-bromo-2-butanone (10), but we succeeded in modifying it. According to the original procedure bromine (100 ml) was added to the mixture of 2-butanone, water and potassium perchlorate at 40-45° with illumination for a period of six hours.

We found that when the temperature of the reaction mixture reached 58°, the decolorization of bromine was instantaneous even without illumination. In this way it was possible to add 210 ml of bromine within one hour.

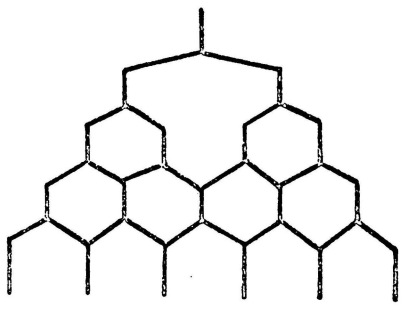
To purify 10 we used a packed 50 cm column, and after a careful distillation over a 2 degree range we obtained a 75 per cent yield of 3-bromo-2-butanone.

Proton nmr indicated that 90 per cent of the mixture was 10 and 10 per cent was 1-bromo-2-butanone.

Treatment of 10 with potassium fluoride in dyglyme at 180-200° gave 3-fluoro-2-butanone (17) in 60 per cent yield.

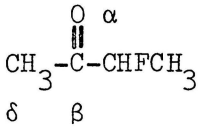
This method is today the most convenient one for the preparation of 17. Furthermore, 10 is very readily converted to 2-bromo-3-fluorobutane (2) which was described earlier.

It is very interesting to observe a long range coupling in ^{19}F nmr (see Figure 1). The basic fluorine nmr of 17 consists of six lines which can be explained in the following way:

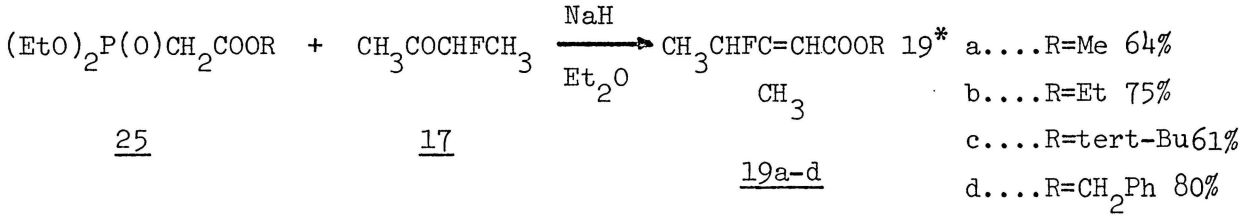


where J_{gem}=50 Hz and J_{vic}=25 Hz.

Expanded to 540 Hz each line is split into a perfect quartet due to the long range coupling of the methyl group γ-to fluorine ($J=5H_z$):



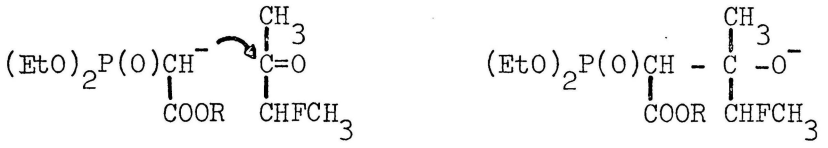
Condensation of diethylphosphonoacetates (25 a,b,c, and d) with 17 under the conditions of the Horner-Emmons reaction[18,19] went smoothly within five minutes and gave 4-fluoro-3-methyl-2-pentenoates (19) in the following yields:



25 17 19a-d

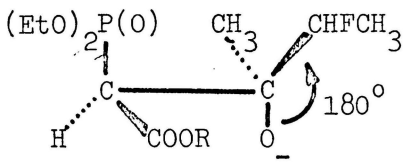
*This designation of esters is consistent throughout the Dissertation.

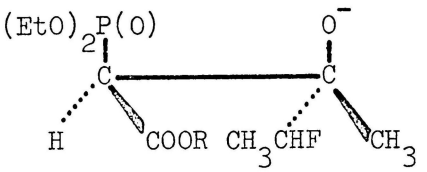
This reaction is stereoselective[30] and proceeds through the following mechanism:



BC

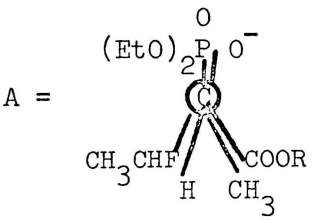
The intermediate BC can exist in two forms:

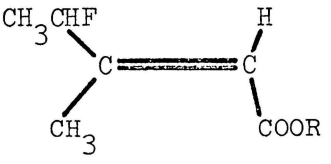




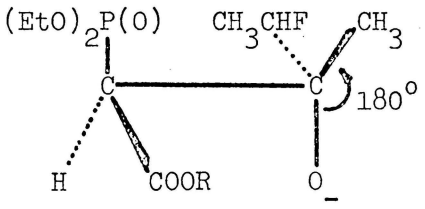
A

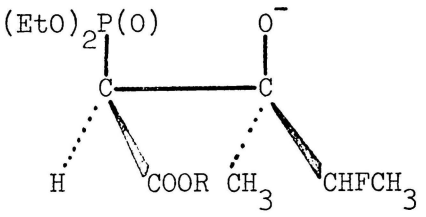
A =





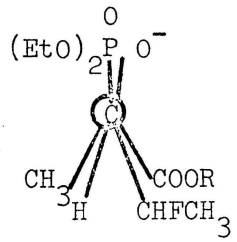
E (trans)

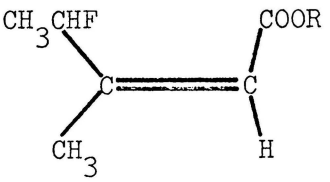

(EtO)2P(O)
CH3CHF
CH3
C
C
180°
H
COOR
O-


(EtO)2P(O)
O-
C
C
H
COOR
CH3
CHFCH3

B

B =

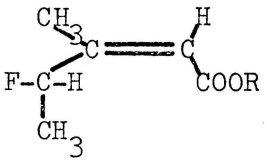

O
(EtO)2P
O-
C
CH3
H
COOR
CHFCH3


CH3CHF
COOR
C
C
CH3
H

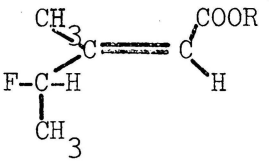
Z(cis)

We obtained the unsaturated esters ranging from 75:25 to 80:20 trans(E) to cis (Z) ratio. This was calculated from proton nmr from the ratios of the two sets of singlets of vinyl protons and the two singlets of the methyl groups.

In fluorine nmr the ratio of E-Z was calculated from the two multiplets:



Z



E

We succeeded in separating the Z-E isomers by simple distillation (see Figures 3-8).

It can be seen that one of the vinyl protons in the proton nmr has disappeared, and at the same time only one singlet of the methyl protons on the double bond showed (see Fig. 6). The detail explanation of the proton nmr of 19 a-d is in Table III (see Appendix).

These results concerning the stereoselectivity of the Horner-Emmons reaction[18,19] are in agreement with the literature.[30,31,32]

As was outlined on page 14, the next step was to reduce the double bond. For catalytic reduction we used rhodium on alumina or on carbon with a catalytic amount of calcium carbonate. This catalyst is superior to palladium on carbon or platinum oxide for the systems where halogen is in a vinylic or allylic position since it does not cause cleavage of the carbon-halogen bond.

The saturated ester was indeed obtained in yields over 90 per cent,

but the attempt to hydrolyze the ethyl ester under basic condition (alcoholic potassium hydroxide) caused dehydrofluorination even at room temperature. Since the acid hydrolysis proceeds with yields less than 50 per cent in similar systems[33] and since another five steps were to be run, we tried to modify this approach.

The most logical way was to prepare esters which can be cleaved under very mild conditions and these are benzyl and tert-butyl esters. The former is cleaved readily by catalytic hydrogenation under neutral conditions (e.g. EtOH-Rh/C), and the latter one under acidic conditions at room temperature.

For that reason we prepared the following phosphonates:

$(EtO)_2P(O)CH_2COOtert\text{-}Bu$ and $(EtO)_2P(O)CH_2COOCH_2Ph$

19c 19d

The tert-butyl and benzyl diethylphosphonoacetates have not been previously described although they have a great advantage over their ethyl analog. One can obtain the free acid by using 19d with an appropriate ketone followed by reduction

$$\underset{\text{19d}}{(EtO)_2P(O)CH_2COOCH_2Ph} + RC(O)R' \longrightarrow R'\underset{R}{C}=CHCOOCH_2Ph$$

Both 19c and 19d are easily prepared by means of the Arbuzov reaction in 74 and 78 per cent yields, respectively.

By using the sequence of reactions described above we obtained 4-fluoro-3-methylpentanoic acid (21) in 60 per cent yield:

$$CH_3CHFC(CH_3)=CHCOOCH_2Ph \xrightarrow[Rh\text{-}C/CaCO_3]{H_2} CH_3CHFCH(CH_3)CH_2COOH$$

21

All attempts to convert 21 into α-bromo acid failed owing to the loss of fluorine.

The Hell-Volhard-Zelinsky reaction[34] was tried with variations in temperature of the reaction between 80-120° but the product contained no fluorine. Another attempt was to use a very mild method for the preparation of α-bromo esters[35] from an acid chloride and N-bromo-succinimide followed by addition of alcohol to the reaction mixture. The first step was followed by proton nmr which showed that the acid chloride was completely formed within one hour (disappearance of the hydroxyl group at 11.5 ppm). Fluorine nmr confirmed the presence of fluorine, but during the treatment of the acid chloride with NBS fluorine was lost.

At that time we did not have a reasonable explanation for the loss of fluorine (whether the NBS replaced fluorine, or dehydrofluorination occurred).

Very recently we found an explanation quite unexpectedly. The acid was distilled usually at the vacuum of the oil pump (between 0.005-0.025 mm) when the acid has a boiling point between 54-60 degrees. Since proton nmr indicated only a slight presence of toluene (from catalytic reduction of benzyl ester) we tried to distill the acid at the vacuum of a water aspirator so as to obtain an analytically pure sample. As soon as the temperature reached 80° vigorous evolution of hydrogen

fluoride started which simply meant that 4-fluoro-3-methylpentanoic acid is thermally unstable at temperatures above 80°. This explains our unsuccessful attempts to prepare the α-bromo acid.

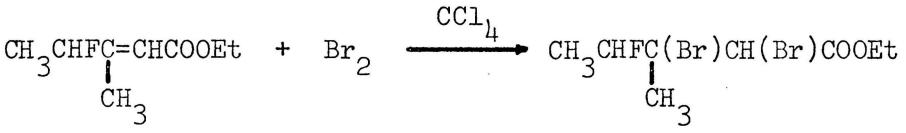
Summary:

1. The Horner-Emmons reaction was used to prepare methyl-, ethyl-, tert-butyl-, and benzyl 4-fluoro-3-methyl-2-pentenoates in high yields.
2. This reaction is stereoselective.
3. Pure E isomer was isolated by distillation.
4. The new phosphonates, tert-butyl and benzyl diethylphosphonoacetates, were prepared as very versatile intermediates in the synthesis of the carboxylic acids.
5. A new synthetic method for the preparation of 3-fluoro-2-butanone (17) has been developed.
6. A long range coupling was observed in the fluorine nmr of 17.
7. 4-Fluoro-3-methylpentanoic acid was found to be thermally unstable.

Project 3

At this point we decided to investigate the possibility of using the ester of 4-fluoro-3-methyl-2-pentenoic acid (19) as a precursor of an α-amino ester. The basic idea was to add across the double bond a group which could be easily converted to the amino function.

Bromine was added across the double bond of 19 within 4 days in almost quantitative yield.

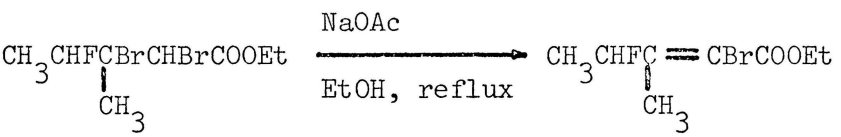


19b 27

The reason for such a slow reaction of bromine is that α,β-conjugated esters are not very reactive toward electrophilic addition.

Next step was to eliminate hydrogen bromide from 27. We tried several recommended reagents for dehydrobromination, like quinoline,[36] lithium chloride in DMF,[37] and a mixture of lithium chloride and lithium carbonate in DMF,[38] but all of these methods lead to a great deal of decomposition.

By far the best method was using sodium acetate in refluxing ethanol for 4 hr:[39]



27 28

The product, ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate, was obtained in 80 per cent yield.

But reduction of that compound presents some very difficult problems owing to the following facts:

1. Bromine is in the vinylic position.
2. Fluorine is in the allylic position.

It is known that halogens in vinylic and allylic positions are cleaved very easily under the conditions of catalytic hydrogenation.

3. The double bond is tetrasubstituted which requires high pressure for reduction.

These factors prevented us from using the benzyl ester of 4-fluoro-3-methyl-2-pentenoic acid (19) since it would be hydrogenolyzed much faster than the double bond would be hydrogenated. Furthermore, it would not be wise to use a tert-butyl ester of 19 which would only increase an already overcrowded double bond.

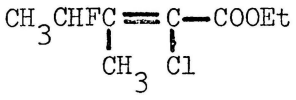
By using the ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate (28) we found that hydrogenation over rhodium on alumina at atmospheric pressure for two days gave the starting material as the only product.

By using 56 atmospheres of hydrogen for another two days the result was the same, no reduction of the double bond occurred. When the pressure of hydrogen was increased to over 75 atmospheres, both fluorine and bromine were eliminated.

Dissolving metal reduction can not be used because bromine would be split out before the attack of the electrons on the double bond.

Since the problems in the reduction of ethyl 2-bromo-4-fluoro-

3-methyl-2-pentenoate (28) were mainly due to the steric hindrance, we tried to use the chlorine analog of 28, ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate (29)

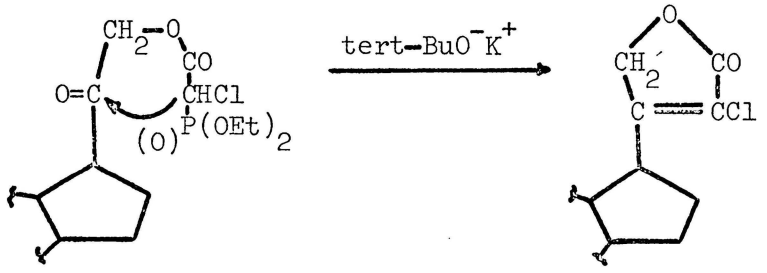


29

which would have two advantages over the bromo compound 28:

- chlorine is smaller than the bromine and it should reduce steric hindrance around the double bond, and
- vinylic chlorine is less prone to cleavage than the bromine.

To prepare 29 we decided to use ethyl diethylphosphonochloroacetate (30) which was used by Eberlein[40] in the following way



Chlorination of ethyl diethylphosphonoacetate (31b) in the presence of an equimolar amount of calcium carbonate gave ethyl 1,1-dichloro-1-diethylphosphonoacetate (32) in 86 per cent yield, as was described by Eberlein.[40]

Reaction of 32 with sodium salt of ethyl diethylphosphonoacetate

in benzene gave 30:

$$(EtO)_2P(O)CCl_2COOEt + (EtO)_2P(O)CH_2COOEt \xrightarrow{NaH} (EtO)_2P(O)\underset{Cl}{CH}COOEt$$

32 31 30

in 33 per cent yield.

But the authors did not mention that the remaining 67 per cent consisted of equal amounts of 31 and 32 which makes purification of the reaction products very difficult. It was necessary to use four successive fractional distillations and the best that we could obtain was a mixture of 30 and 32 in the ratio of 90:10.

We used that mixture for condensation with 3-fluoro-2-butanone, and obtained ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate (29) in 63 per cent yield.

$$(EtO)_2P(O)CHClCOOEt \xrightarrow[\text{benzene}\\ \text{NaH}]{CH_3COCHFCH_3} CH_3CHFC(CH_3)=CClCOOEt$$

30 29

Unfortunately, all attempts to reduce 29 failed. Our next attempt was to introduce a nitro group into ethyl 4-fluoro-3-methyl-2-pentenoate (19b). Nitration of alkenes with nitric acid has been known for over 130 years but very often a complex mixture of products is obtained.[41]

Some derivatives of nitric acid have been proved to be of much greater value, particularly nitrogen oxides[42,43] although each one has some disadvantage (e.g. use of nitrogen (IV) oxide suffers from tedious processing of products and use of nitrogen (V) oxide is limited by its

relative inaccessibility).

Bordwell and Garbisch[44] successfully applied a mixture of acetic anhydride-nitric acid for nitration of mono-, di-, tri-, and tetra-substituted alkenes under very mild conditions (-12° for 5 minutes). The nitrating species is nitronium-acetate complex:

$$CH_3COO^-NO_2^+$$

which we tried to use in the following way

$$CH_3CHFC(CH_3)=CHCOOR \xrightarrow[HNO_3]{Ac_2O} CH_3CHFC(CH_3)(OAc)CH(NO_2)-COOR$$

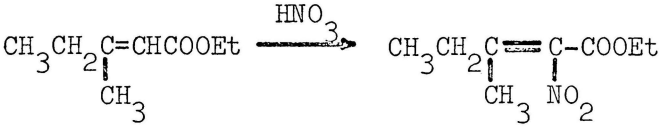
$$\xrightarrow[\text{or base}]{\text{heat}} CH_3CHFC(CH_3)=C(NO_2)-COOR$$

With the benzyl ester (19d) nitration of the benzene ring occurred rather than the addition across the double bond. When ethyl ester (19b) was used instead, only the starting material was recovered.

It must be emphasized that this method suffers from several disadvantages. First, the temperature must be maintained below 40° otherwise an exothermic reaction occurs. Unfortunately, one can not use prolonged reaction times to make up for lower temperatures because after three hous the concentration of nitronium ion is significantly decreased.[44]

Later we decided to use nitric acid as the nitrating agent. We found several references[45,46,47] where nitric acid was used in the synthesis of amino acids but each reference listed different experimental

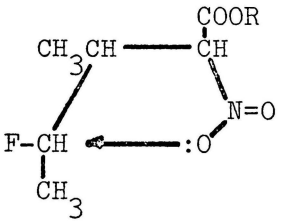
conditions. Therefore we decided to conduct some model experiments to determine the best temperature and reaction time for our system. Ethyl 3-methyl-2-pentenoate was prepared by means of the Horner-Emmons reaction[18,19] and was used for the model experiment.

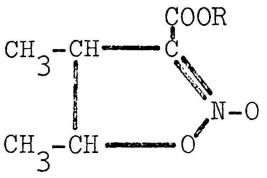


The best conditions were to keep the temperature between 17 and 20° during the addition of the α,β-conjugated ester and then at 30° for 6 hr. The desired product obtained in 30 per cent yield was identified by proton nmr and characteristic ir.

Reproducing nitration with ethyl 4-fluoro-3-methyl-2-pentenoate under the very same conditions we obtained a product containing no fluorine.

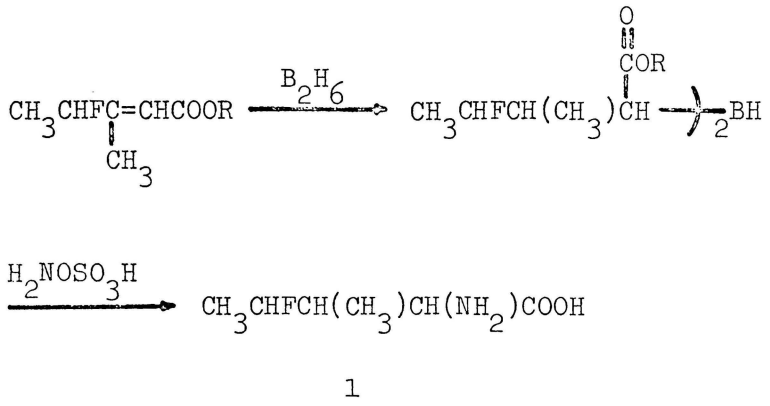
One way to explain this is that the nitro group can eliminate fluorine in the following way:





But this is only a speculation without any spectral evidence since we have not been able to interpret the proton nmr spectrum of the product.

Another idea that occurred to us was to use the method developed by Brown[48] for the preparation of amines via hydroboration and to apply it to the synthesis of amino acids:



1

Several attempts failed and we abandoned this idea.

We also tried to add nitrosyl chloride across the double bond but after 4 days no reaction occurred, and only the starting material was recovered.

Summary:

1. The following novel compounds have been prepared:
   ethyl 2,3-dibromo-4-fluoro-3-methylpentanoate (27),
   ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate (28) and
   ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate (29).
2. The double bond in 28 and 29 could not be reduced by means of catalytic hydrogenation under a pressure of hydrogen below 56 atmospheres. When the pressure was increased over 70 atmospheres, fluorine was eliminated from 28 and 29.
3. Attempts to introduce nitro group into 19 by means of nitric acid or nitryl acetate failed.
4. An attempt to add nitrosyl chloride across the double bond in 19 failed.

Project 4

Our further attempt was to prepare ethyl 2-ethoxycarbonyl-4-fluoro-3-methylpentanoate (3) or ethyl 2-acetyl-4-fluoro-3-methylpentanoate (33) by some other means than C-alkylation which did not work (see Project 1).

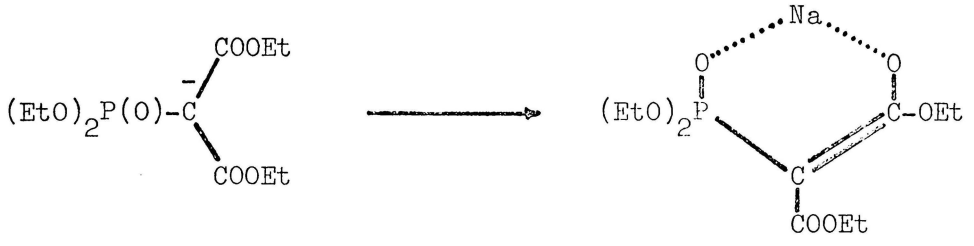
One of the most logical ways to start this project was to use the Knoevenagel reaction (or the Doebner modification of it).[49] When we attempted condensation between 3-fluoro-2-butanone and diethyl malonate or ethyl acetoacetate with different bases, only the starting material was obtained. Since we had good experience with the Horner-Emmons reaction we tried to use it here in a slightly modified way.

Bromination of diethylmalonate gave diethyl bromomalonate (34) in 60 per cent yield as described in the literature.[50] The Arbuzov reaction of 34 with triethylphosphite produced tetraethylphosphonomalonate (35) as described in the literature:[51]

$$CH_2(COOEt)_2 + Br_2 \xrightarrow{NaOH} \underset{34}{CHBr(COOEt)_2}$$

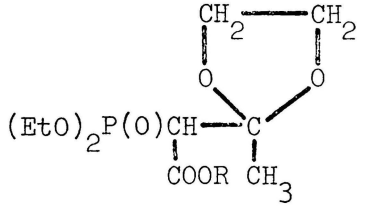
$$\underset{}{(EtO)_3P} \longrightarrow \underset{35}{(EtO)_2P(O)CH(COOEt)_2}$$

The condensation between 35 and 3-fluoro-2-butanone did not give the expected product. Instead, the carbanion once formed did not react further, probably due to the stability of the intermediate:



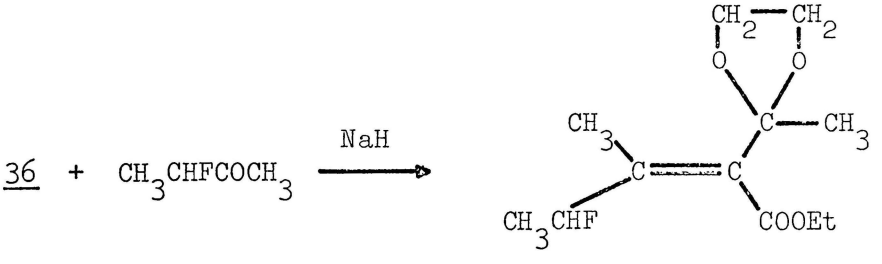
A very similar intermediate has been described elsewhere.[52]

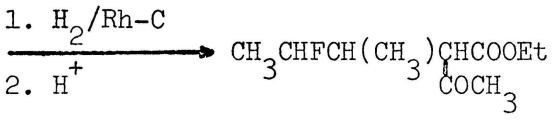
One way to avoid enolization of the anion would be to remove one of the carbonyl groups. To achieve this we tried to prepare ethyl 1-diethylphosphono-1-acetylacetate ethylene ketal (36)



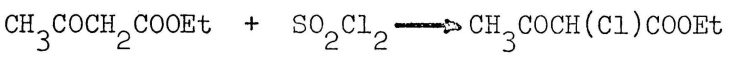
36

which could give 3-ethoxycarbonyl-5-fluoro-4-methyl-2-hexanone in three steps:



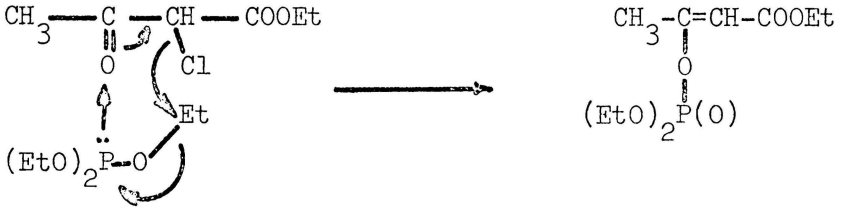


As the starting material we decided to use ethyl α-chloroacetoacetate (37) which is readily prepared from the reaction of sulfuryl chloride and ethyl acetoacetate[53]

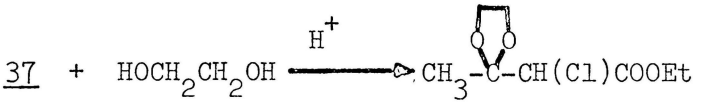


37

Since ethyl α-chloroacetoacetate (37) can not undergo Arbuzov rearrangement but rather Perkow reaction[54]



we first had to protect the carbonyl group:

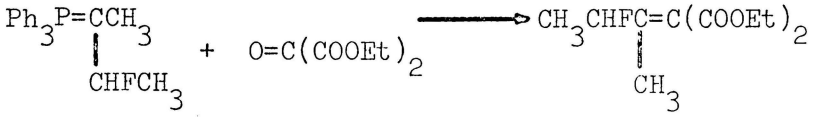


36

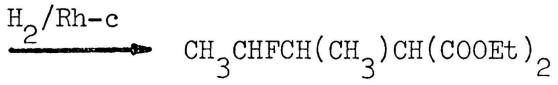
That was achieved by using p-toluenesulfonic acid as a catalyst and ethylene glycol. The product (36) was obtained in 45 per cent yield. But 36 did not undergo the Arbuzov reaction even after heating the mixture at 150° for two days. The only reasonable explanation is that steric hindrance around C-2 prevents the rearrangement.

Another way to prepare ethyl 2-ethoxycarbonyl-4-fluoro-3-methylpentanoate (3) would be the Wittig reaction between diethyl mesoxalate (39) and 3-fluoro-2-butylidene triphenylphosphorane (38), followed by

reduction of the intermediate (40):



38 39 40



3

Oxidation of diethylmalonate with nitrogen (III) oxide afforded diethyl mesoxalate in 40 per cent yield as described[55] but all attempts to prepare 38 from 2-bromo-3-fluorobutane (2) and triphenylphosphine failed and the same results were obtained as in the case of attempted alkylation of malonates with 2

- if the temperature was below 110° only starting material was recovered;
- if the temperature was increased over 110° an elimination of fluorine occurred.

Summary:

1. Tetraethylphosphonomalonate does not undergo the Horner-Emmons reaction with ketones.
2. Ethyl 1-acetyl-1-diethylphosphonoacetate ethylene ketal does not react with triethylphosphite under the conditions of the Arbuzov

reaction.

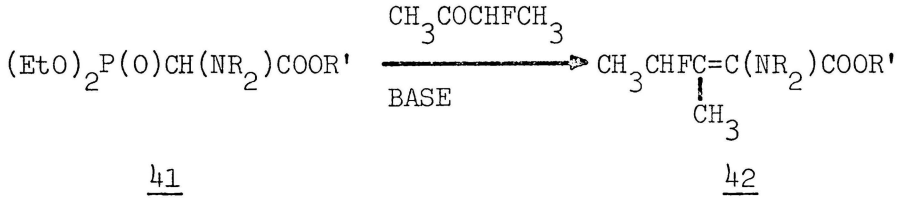
3. Bromine in 2-bromo-3-fluorobutane can not be displaced with triphenylphosphine.

Project 5

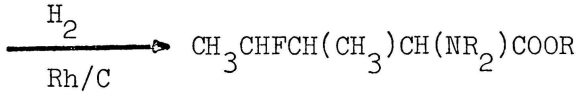
Having so many unexpected problems in the synthesis of γ-fluoro-isoleucine (1) even with methods that work under very mild conditions we decided to try to simplify the synthesis even more.

So far we knew that condensation of 3-fluoro-2-butanone with diethylphosphonoacetates (25a-d) proceeded very smoothly but the problem was to introduce the amino group into the α-position.

If we could introduce the amino group into the phosphonate prior to the condensation it would require only one step to make an amino acid:



41 42



43

It can be easily seen that since the N-protecting group and the ester function could be cleaved under the conditions of catalytic hydrogenation, benzyl 1-dibenzylamino-1-diethylphosphonoacetates would be a universal reagent for the preparation of amino acids in one step.

The most convenient compound to prepare would be benzyl 1-N,N-dibenzylamino-1-diethylphosphonoacetate (41a)

$(EtO)_2P(O)CH(N(CH_2PH)_2)-COOCH_2Ph$ 41 a when R=R'=CH_2Ph

41 b R=R'=tert-Bu

because N-benzyl and O-benzyl groups are easy to cleave by catalytic hydrogenation.

Surveying the literature, we found that Gross[56] used methyl 1-piperidino-1-diethylphosphonoacetate (44) to prepare the α-keto acids

$$(EtO)_2P(O)CH(N(CH_2)_5)-COOMe + ArCHO \xrightarrow[\text{glyme}]{NaH} ArCH=C(N(CH_2)_5)-COOMe$$

44 Enamine

$$\text{Enamine} + H^+, H_2O \longrightarrow ArCH_2COCOOMe$$

Several publications concerning the preparation of 44 have appeared from the same German group.[57-61] We first tried the one which looked the most convenient, starting with dichloroacetic acid:

$$Cl_2CHCOOH \xrightarrow[MeOH]{NaOMe} (MeO)_2CHCOONa \xrightarrow[2.\ MeOH]{1.\ SOCl_2} (MeO)_2CHCOOMe$$

45 46

$$\xrightarrow{PCl_5} MeOCH(Cl)COOMe + POCl_3$$

47

We followed the described procedure[56] and obtained methyl 1-chloro-1-methoxyacetate (47) in 75 per cent yield. The next step was to add

$$CH_3OCH(Cl)COOCH_3 + 2HN(CH_2)_5 \xrightarrow[-78^\circ]{Et_2O} CH_3OCH(N(CH_2)_5)-COOCH_3 + H_2\overset{+}{N}(CH_2)_5Cl^-$$

47 48

and the desired product, methyl 1-piperidino-1-methoxyacetate, was obtained in 65 per cent yield as described.[58]

The first problem was to prepare the benzyl or tert-butyl ester of 47 rather than the methyl ester, mainly because of difficulties involved in hydrolysis of the methyl ester. Surveying the literature we found the preparation of tert-butyl 1-bromo-1-methoxyacetate by Carpino[62] starting from methoxyacetic acid:

$$CH_3OCH_2COOH + CH_3C(CH_3)=CH_2 \xrightarrow{H^+} CH_3OCH_2COOC(CH_3)_3$$

49

$$\xrightarrow[CCl_4, \text{reflux}]{NBS} CH_3OCH(Br)COOC(CH_3)_3$$

50

We prepared 50 in 78 per cent yield. This procedure is far more elegant than the one described by Gross[56] and has two advantages:

1. tert-butyl ester is very easy to cleave under acidic conditions, and
2. bromine is very easy to displace by nucleophiles.

All attempts to use ammonia and tert-butyl 1-bromo-1-methoxyacetate (50) failed and gave a mixture of several products which could

not be identified. Using benzylamine as another possibility failed too, so we decided to use N,N-dibenzylamine:

$$CH_3OCH\text{-}COOC(CH_3)_3 + (PhCH_2)_2NH \xrightarrow[-78^\circ]{Et_2O} CH_3O\underset{\displaystyle N(CH_2Ph)_2}{\underset{|}{C}}H\text{-}COOC(CH_3)_3$$

51

Several attempts to prepare 51 failed at first, but finally we obtained tert-butyl 1-methoxy-1-N,N-dibenzylaminoacetate (51) in a quantitative yield. The important factor was to have a large excess of a solvent (e.g. for 20g of 50, 500ml of ester), to keep the temperature at -78°, and to add dibenzylamine very slowly (about 2 hr for 15 g of amine). The product was a thick oil which could not be distilled because of decomposition. The structure was established by proton nmr spectrum.

All these difficulties in using 50 to prepare 51 were probably due to the great reactivity of bromine.

Having 51 successfully prepared we had to convert it now into the diethylphosphono derivative using the following reaction:

$$51 + (EtO)_2P(O)H \xrightarrow[-CH_3OH]{heat} (EtO)_2P(O)CH\text{-}COOC(CH_3)_3$$

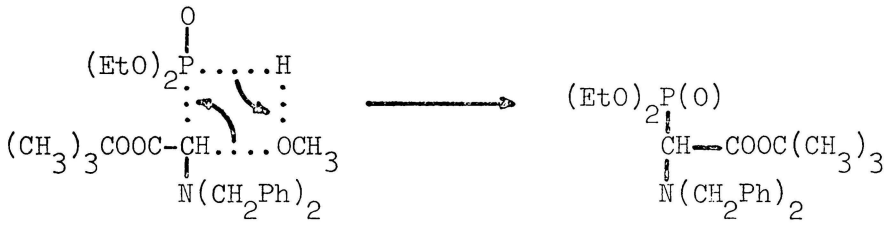
41b

An analogous reaction was described previously by Gross[59] using 44 and diethylphosphite:

$$CH_3O\underset{\displaystyle N(CH_2)_5}{\underset{|}{C}}H\text{-}COOCH_3 + (EtO)_2P(O)H \xrightarrow{80^\circ} (EtO)_2P(O)\underset{\displaystyle N(CH_2)_5}{\underset{|}{C}}HCOOCH_3$$

44

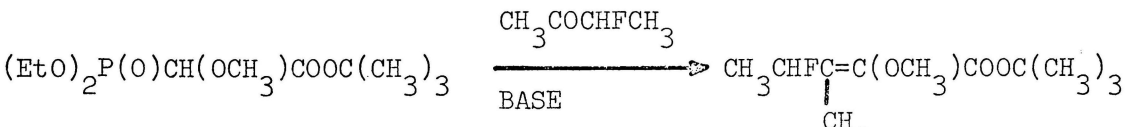
All the attempts to convert tert-butyl 1-N,N-dibenzylamino-1-methoxy-acetate (51) into the tert-butyl 1-N,N-dibenzyl-1-diethylphosphonoacetate, even after 24 hr of heating at 100° failed, and only the starting materials were recovered. This is probably due to the steric problems in the transition state which has to achieve a coplanar-four center intermediate:



41b

The tert-butyl ester makes the α-carbon rather hindered for which we have experimental evidences (see Project 7).

So far, we have not been able to prepare phosphonates bearing carboxyl- and amino-function at the same time. Another option was to use phosphonates like 1-diethylphosphono-1-methoxyacetate which would give vinyl ether as a product when condensed with 3-fluoro-2-butanone:



52 53

The resulting tert-butyl 4-fluoro-2-methoxy-3-methyl-2-pentenoate (53) would give in one step 4-fluoro-2-keto-3-methylpentanoic acid (54) under acidic conditions:

$$\underline{53} + H^+, H_2O \longrightarrow CH_3CHFC(CH_3)\underset{\underset{O}{\|}}{C}\text{-}COOH$$

$\underline{54}$

Treatment of $\underline{54}$ with benzylamine followed by reduction (so called reductive amination)[63] would give $\underline{1}$

$$\underline{54} \xrightarrow[2.\ H_2/Pd\text{-}C]{1.\ PhCH_2NH_2} CH_3CHFCH(CH_3)CH(NH_2)COOH$$

$\underline{1}$

We prepared tert-butyl 1-diethylphosphono-1-methoxyacetate (52) in 85 per cent yield following the procedure described by Gross [60] in which methyl 1-chloro-1-methoxyacetate was used as a starting material:

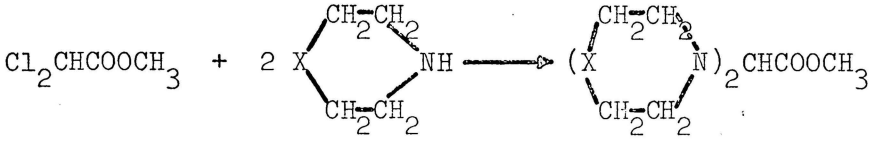
$$CH_3OCH(Br)COOC(CH_3)_3 + (EtO)_3P \longrightarrow (EtO)_2P(O)CH(OCH_3)COOC(CH_3)_3$$

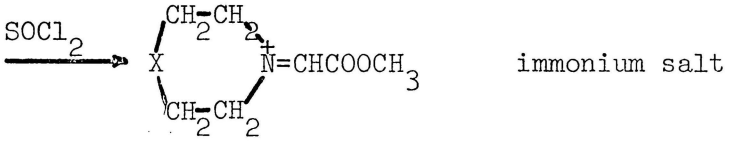
$\underline{52}$

The condensation step between $\underline{52}$ and 3-fluoro-2-butanone is still a mystery to us because we do not know what happened to cause severe decomposition during the work up of the reaction mixture. We know that the anion of $\underline{52}$ was formed by following the evolution of hydrogen. The fluoro ketone was then added and after 1 hr the reaction mixture was quenched with water. The product was distilled and a proton nmr spectrum was in a very good agreement with that of the expected product, tert-butyl 4-fluoro-2-methoxy-3-methyl-2-pentenoate. A few minutes later a sever decomposition of the product occurred with evolution of hydrogen fluoride. The proton nmr spectrum of the decomposed mixture could not be interpreted.

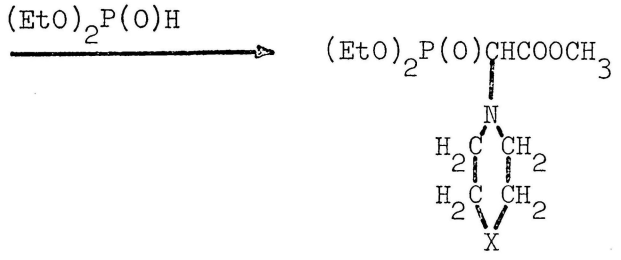
We tried to avoid decomposition by quenching the reaction product with diluted acid, hoping to obtain 4-fluoro-2-keto-3-methylpentanoic acid without isolation of the vinyl-ether intermediate. Unfortunately, this attempt failed and only a fluorine-free product could be obtained.

Another possibility to introduce the diethylphosphono group into the molecule is to add diethylphosphite across the double bond. By adding diethylphosphite across the double bond of animmonium salt, Gross[58] prepared the following compound:





immonium salt



We prepared benzyl dichloroacetate in 70 per cent yield, from dichloroacetylchloride and benzyl alcohol, and attempted the same sequences of reactions:

$$Cl_2CHCOOCH_2Ph + (PhCH_2)_2NH \xrightarrow{SOCl_2} (PhCH_2)_2\overset{+}{N}=CHCOOCH_2Ph$$

immonium salt

$$\text{immonium salt} + (EtO)_2P(O)H \longrightarrow (EtO)_2P(O)\underset{\displaystyle N(CH_2Ph)_2}{\underset{|}{CH}}-COOCH_2Ph$$

41a

A very complex mixture was obtained so we tried to prepare a Schiff base of similar structure.

Schiff bases are relatively easy to prepare and most of them are fairly stable compounds. Furthermore, we believe that the main reason we could not introduce diethylphosphono group into tert-butyl 1-N,N-dibenzylamino-1-diethylphosphonoacetate (51) was due to a steric problem. Since a Schiff base is a planar (sp^2) hybrid this should eliminate undesirable steric factors.

The Schiff base we need should look like

R-N=CHCOOR

From the work of Carpino[62] we knew that tert-butyl 1-methoxy-1-bromo-acetate can be converted into tert-butylglyoxalate

$$CH_3OCH(Br)COOC(CH_3)_3 \xrightarrow[H_2O]{NaHCO_3} OHC-COOC(CH_3)_3$$

55

Furthermore, the conversion of Schiff's bases into diethylphosphono derivatives has been successfully used elsewhere:[64]

$$ArCH{=}NAr + (EtO)_2P(O)H \xrightarrow{\text{base}} (EtO)_2P(O)CH(Ar)NHAr$$

Having prepared tert-butyl glyoxalate in 44 per cent yield, we attempted the preparation of the Schiff base and the addition of diethylphosphite:

$$OHCCOOC(CH_3)_3 + PhCH_2NH_2 + (EtO)_2P(O)H \longrightarrow \text{mixture}$$

We tried this reaction in several different ways but only a very complex mixture could be obtained (see experimental section). The reasons for the complexity of the reaction could be several:

- if the desired Schiff base was formed initially, it could isomerize

$$PhCH_2N{=}CHCOOC(CH_3) \rightleftharpoons PhCH{=}N{-}CH_2COOC(CH_3)_3$$

- it is known that lower aliphatic Schiff's bases polymerize very easily (form a dimers):

$$2\ R{-}N{=}CH{-}R \longrightarrow \begin{array}{c} R{-}CH{-}N{-}R \\ | \quad | \\ R{-}N{-}HC{-}R \end{array}$$

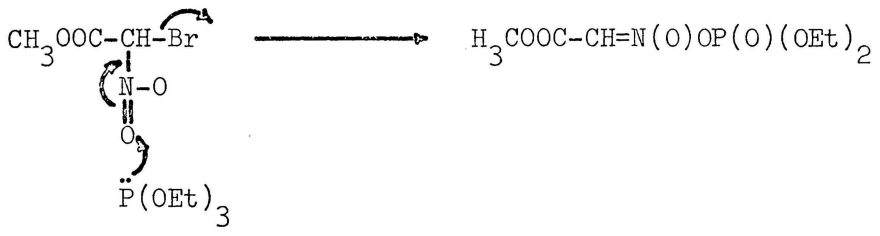
One more attempt was made to react ethyl 1-bromo-1-nitroacetate (56) with triethylphosphite under the conditions of the Arbuzov reaction. Starting material 56, was prepared in 58 per cent yield as described in the literature[65]

$$O_2N{-}CH_2{-}COOCH_3 + Br_2 \xrightarrow{NaOCH_3} O_2NCH(Br)COOCH_3$$

56

$$\xrightarrow{(EtO)_3P} (EtO)_2P(O)CH(NO_2)COOCH_3$$

During the course of the Arbuzov rearrangement a very complex mixture was formed. Similar discovery was reported elsewhere[66,67] and it is suspected that one of the products is a result of Perkow rearrangement (or so called "abnormal Arbuzov rearrangement")



Summary:

1. A novel compound, tert-butyl 1-N,N-dibenzylamino-1-methoxyacetate (51) was prepared in a quantitative yield using tert-butyl 1-bromo-1-methoxyacetate as a starting material.
2. All attempts to convert 51 into tert-butyl 1-diethylphosphono-1-N,N-dibenzylaminoacetate by using diethyl phosphite failed probably due to steric problems.
3. A novel compound, tert-butyl 1-diethylphosphono-1-methoxyacetate (52) was prepared from tert-butyl 1-bromo-1-methoxyacetate and triethylphosphite by way of the Arbuzov rearrangement.
4. Condensation of 52 with 3-fluoro-2-butanone proceeded as expected, initially, to give tert-butyl 4-fluoro-2-methoxy-3-methyl-2-pentenoate but the compound decomposed on standing for which we do

not have any explanation.

5. Attempt to prepare tert-butyl 1-diethylphosphono-1-N-benzylamino-acetate from tert-butylglyoxalate, benzylamine, and diethyl-phosphite were not successful.

6. Reaction of methyl 1-bromo-1-nitroacetate with triethylphosphite is suspected to undergo the Perkow rearrangement.

Project 6

Aiming at the synthesis of a "universal reagent" for the amino acid synthesis we found that it is possible to use dialkylphosphites in a Mannich-type manner:[68]

$$(RO)_2P(O)H + HCHO + R'_2NH \longrightarrow (RO)_2P(O)CH_2NR'_2$$

We could use 57 and carboxylate it employing chloroformate as a source of the carboxyl group:

$$57 + ClCOOR \xrightarrow{Base} (RO)_2P(O)\underset{\displaystyle NR'_2}{\underset{|}{C}}H\text{-}COOR$$

Using diethylphosphite, dibenzylamine, and formaldehyde we did not obtain 57 but bis-N,N-dibenzylaminomethane as the only product. The structure was established by its proton nmr spectrum and independent synthesis of the same compound using only dibenzylamine and formaldehyde:

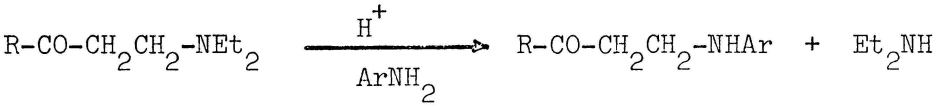
$$2\ (PhCH_2)_2NH + HCHO \longrightarrow (PhCH_2)_2N\text{-}CH_2\text{-}N(PhCH_2)_2$$

This came as a surprise since diethylamine, diethylphosphite and formaldehyde gave high yields of diethyl N,N-diethylaminomethylphophonate,[68] and we have been able to reproduce it:

$$(EtO)_2P(O)H + HCHO + Et_2NH \longrightarrow (EtO)_2P(O)CH_2NEt_2$$

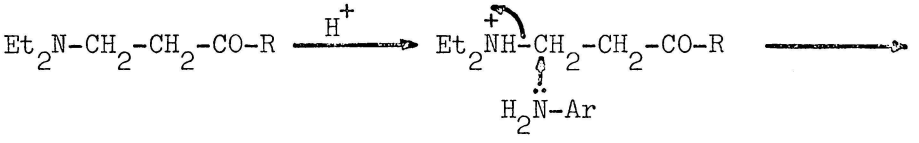
57b

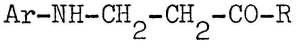
Although 57b was not the desired product, we found that it is possible to exchange the diethylamino group for aromatic amines under acidic conditions:[69]



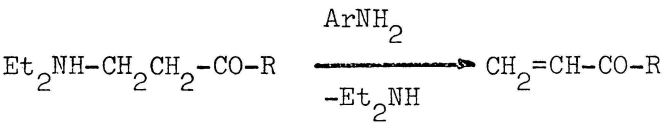
Originally, this reaction was designed to prepare Mannich products with aromatic amines which by themselves cannot undergo a Mannich reaction because formylation of the aromatic nuclei is the dominant reaction. The authors[69] proposed two mechanisms for the exchange step:

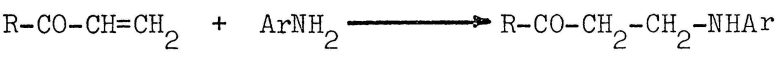
Mechanism A.....substitution:





Mechanism B.....elimination-addition:





We decided to investigate the use of diethyl N,N-diethylaminomethyl-phosphonate (57b) as a starting material in the exchange reaction with dibenzylamine:

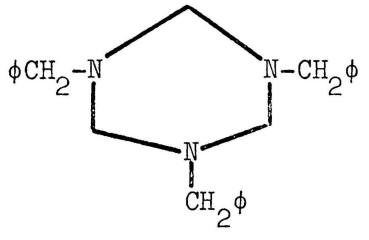
$$(EtO)_2P(O)CH_2NEt_2 \xrightarrow[H^+]{(PhCH_2)_2NH} (EtO)_2P(O)CH_2\text{-}N(CH_2Ph)_2$$

57d

The exchange reaction did not occur and only the starting material could be recovered.

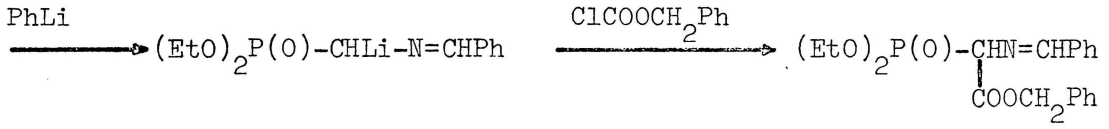
If the operating mechanism of the exchange reaction is Mechanism A-(substitution), we should be able to exchange the diethylamino-group for a dibenzylamino group under acidic conditions, since diethylamine is a stronger base and would be protonated first. Furthermore, 57b cannot possibly undergo elimination-addition type mechanism (Mechanism B) because there is no β-hydrogen in 57b available for β-elimination. The fact that no exchange occur red between 57b and dibenzylamine strongly indicates that the operating mechanism is the elimination-addition (Mechanism B).

Confirmation that our idea of preparing benzyl 1-diethylphosphono-1-N,N-dibenzylaminoacetate (41a) was a good one may be found in a very recent publication[70] describing preparation of benzyl 1-diethylphosphono-1-N-benzalaminoacetate starting from 1,3,5-hexahydro-1,3,5-tribenzyl-triazine:

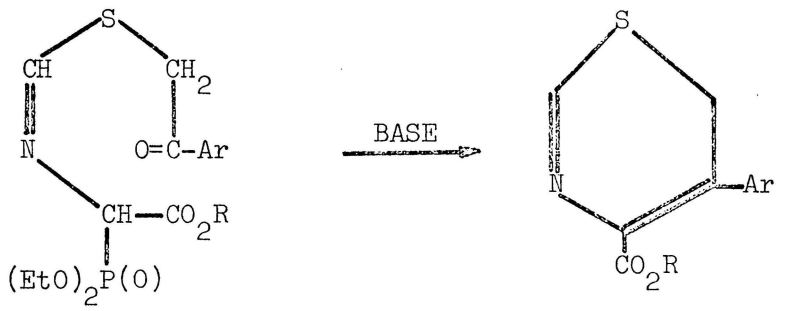


$$+ \ (EtO)_3P \longrightarrow 3(EtO)_2P(O)CH_2NHCH_2Ph$$

$$\xrightarrow{H_2} (EtO)_2P(O)CH_2NH_2 \xrightarrow{PhCHO} (EtO)_2P(O)CH_2N{=}CHPh$$



The product obtained was used in the synthesis of a heterocyclic compound which had an "enamine intermediate" that we proposed:



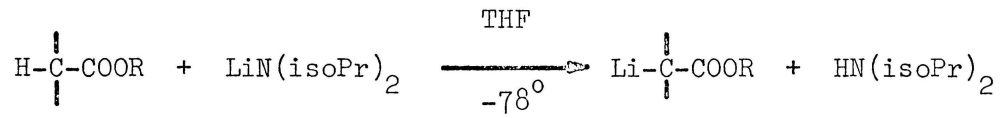
Due to the fact that preparation of II is very tedious, that the experimental part describing the final condensation step[71] is more than obscure, and that in the meantime we found a procedure for the preparation of the desired amino acid in a relatively simple way, we did not proceed further with this project.

Summary:

1. The reaction between dibenzylamine, diethyl phosphite, and formaldehyde gave bis-N,N-dibenzylaminomethane as the only product.
2. The diethylamino group in diethyl N,N-diethylaminomethylphosphonate cannot be exchanged for the dibenzylamino group.

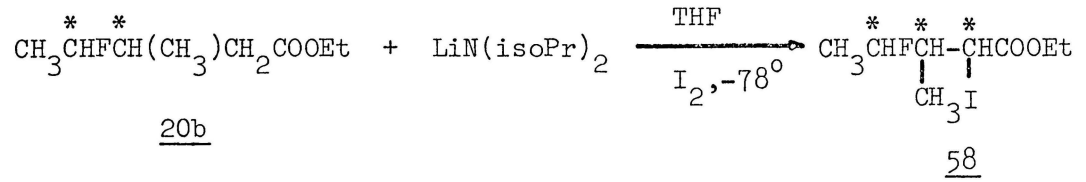
Project 7

Very recently we came across a publication of Rathke[72] in which he describes halogenation of lithium ester enolates using lithium N,N-diisopropyl-or N-cyclohexyl-N-isopropyl-amide and bromine or iodine at low temperatures:



This method looked very attractive to us because we can prepare esters of 4-fluoro-3-methylpentanoic acid in high yields starting from 3-fluoro-2-butanone and alkyl diethylphosphonoacetates.

First, we prepared ethyl 2-iodo-4-fluoro-3-methylpentanoate in 15 per cent yield, by adding ethyl 4-fluoro-3-methylpentanoate to the lithium N,N-diisopropylamide in tetrahydrofuran at -78°. The lithium ester enolate was added to iodine in THF at -78° and the mixture was then quenched with water. The product shows four sets of peaks in ^{19}F nmr spectrum because it has three chiral centers and therefore 4 pairs of enantiomers:



20b

58

Bromination of 20b proceeded in the same fashion and gave ethyl 2-bromo-4-fluoro-3-methylpentanoate (22b) in 16.6 per cent yield.

In the same manner we prepared methyl- and tert-butyl 2-bromo-

4-fluoro-3-methylpentanoate:

$CH_3\overset{*}{C}HF\overset{*}{C}H(CH_3)\overset{*}{C}H(Br)COOMe$ $CH_3\overset{*}{C}HF\overset{*}{C}H(CH_3)\overset{*}{C}H(Br)COOtert\text{-}Bu$

22a 22c

The next step was to introduce the azido group:

$$CH_3CHFCH(CH_3)CH(Br)COOR + NaN_3 \longrightarrow CH_3CHFCH(CH_3)CH(N_3)COOR$$

22 23

This was achieved by refluxing a mixture of 22 and sodium azide in methanol;[73,74] 23 was obtained in very high yields. When tert-butyl ester was used, it was necessary to heat the mixture of 22c and sodium azide in methanol for 48 hr to prepare 23c in a quantitative yield. The additional time required for the preparation of 23c was probably due to the bulkines of the tert-butyl group.

Catalytic hydrogenation of 23 yielded ethyl- and tert-butyl 2-amino-4-fluoro-3-methylpentanoate in 60 per cent yield:

$$CH_3CHFCH(CH_3)CH(N_3)COOR \longrightarrow CH_3CHFCH(CH_3)CH(NH_2)COOR$$

23 24

For the hydrogenation of ethyl 2-azido-4-fluoro-3-methylpentanoate it was enough to apply only 4 atm pressure of hydrogen, and 24b was obtained in 60 per cent yield. To reduce the tert-butyl ester of 2-azido-4-fluoro-3-methylpentanoic acid, we had to increase the pressure of hydrogen up to 40 atm.

The amino esters, ethyl 2-amino-4-fluoro-3-methyl-pentanoate (24b) and tert-butyl 2-amino-4-fluoro-3-methylpentanoate (24c) have been characterized by proton and fluorine nmr spectra and infra red spectra.

The final step was acid hydrolysis of the tert-butyl ester:

$$CH_3CHFCH(CH_3)CH(NH_2)COOtert\text{-}Bu \xrightarrow{CF_3COOH} CH_3CHFCH(CH_3)CH(NH_2)COOH$$

24c 1

The hydrolysis was completed by stirring 24c in trifluoroacetic acid overnight.[75] A white crystalline product was obtained which is soluble in water, contains fluorine, and shows a positive ninhydrin test. Due to the fact that only a very small amount of this material was obtained we do not have at the moment enough material for the proper C,H,N, and F analysis.

Summary:

1. The novel compounds have been prepared: methyl-, ethyl-, and tert-butyl 2-bromo-4-fluoro-3-methylpentanoates.
2. Treatment of the mentioned compounds with sodium azide in methanol gave methyl-, ethyl-, and tert-butyl 2-azido-4-fluore-3-methylpentanoates, respectively, in very high yields.
3. Catalytic hydrogenation of the azido-compounds gave ethyl- and tert-butyl 2-amino-4-fluoro-3-methylpentanoates.
4. Trifloroacetic acid hydrolysis of tert-butyl 2-amino-4-fluoro-3-methylpentanoate gave a crystallinic compound which contained

fluorine, was water-soluble, and showed a positive ninhydrin test. Not enough of that material has been prepared for the proper C,H,N and F analysis.

EXPERIMENTAL

General

Boiling points are uncorrected. Pressure is reported in millimeters of mercury. Weights of samples and products are reported in grams (g) and volumes of samples in liters (l) or milliliters (ml).

Nuclear magnetic resonance (nmr) spectra were obtained using JEOL-PS-100 High Resolution NMR. The carbontetrachloride was used as the solvent.

Hexafluorobenzene was standard for all ^{19}F nmr spectrums and peaks upfield from it had negative sign.

Infrared spectra were recorded with a Beckman IR-20 AX infrared spectrophotometer. Sodium chloride plates were used for the liquids.

Gas chromatographic analyses were carried out on a Varian-Aerograph 920 chromatograph with thermal conductivity detector. 5'x1/4' stainless steel column packed with 3% SE-30 on 100/120 Varaport 3 was employed. Helium was used as the carrier gas with a flow rate of 60 ml/min.

All chemicals were commercial reagent grade unless otherwise specified, and were used without further purification.

1.1 Preparation of 3-bromo-2-butanol (7)[12]

Method A

To 132 ml of 48 per cent hydrobromic acid, 50 g (0.694 mole) of 2,3-epoxybutane was added so that the temperature did not exceed 5°. After 1 hr, the mixture was extracted with methylene chloride, washed with aqueous sodium carbonate, and dried over magnesium sulfate. Distillation through a short (10 cm) Vigreux column gave 85 g (80%) of 7: bp 62-65° (21 mm)

^{1}H nmr δ4.15 (m,1,CHBr), 3.7 (m,1,CHOH), 1.95 (s,1,CHOH), 1.7 (t,3,CH_3CHOH), and 1.25 (d,3,CH_3CHBr).

Method B

To a suspension of 1.51 g (0.04 mole) of lithium aluminum hydride (LAH) in 100 ml of ether, 22.0 g (0.146 mole) of 3-bromo-2-butanone was added with ice-water bath cooling. The mixture was refluxed for 1 hr and then the excess of LAH was decomposed with 25 ml of 10 per cent sulfuric acid. The ethereal layer was dried over magnesium sulfate and 7 was obtained in 56 per cent yield: bp 49-54° (13 mm).

1.2 Preparation of 2-chloro-1,1,2-trifluorotriethylamine (9)[13]

To 110 ml (1.07 mole) of diethylamine, precooled to -78° in an autoclave by means of a Dry Ice-acetone bath, 145 g (1.24 mole) of condensed 2-chloro-1,1,2-trifluorocthylene was added all at once. The autoclave was closed and left at room temperature for 4 hr. The product was obtained in 81 per cent yield (166 g): bp 50-51° (14 mm).

^{1}H nmr δ6.5 (quartet$_{J_{gem}50Hz, J_{vic}25Hz}$, 1, $\underline{CH}ClF$), 3.22 (quartet, 4, N-$\underline{CH_2}CH_3$), and

1.40 (t, 6, N-$CH_2\underline{CH_3}$).

1.3 Preparation of 2-bromo-3-fluorobutane (2)[13]

To 85 g (0.556 mole) of 3-bromo-2-butanol in 250 ml of ether, 20 ml of 2-chloro-1,1,2-trifluorotriethylamine was added. The resulting mixture which warmed during the addition was stirred vigorously, and then the rest of 9 (106 g = 0.56 mole total) was added. The solution was stirred for 24 hr at room temperature and then washed three times with water, once with aqueous sodium bicarbonate, and dried over magnesium sulfate. The ethereal layer was concentrated to leave 46.5 g (54.4 per cent yield) of 2: bp 38-39° (70 mm).

^{1}H nmr δ 4.5 (pair of $m_{J=50Hz}$, 1, $\underline{CH}F$), 4.0 (m, 1, $\underline{CH}Br$), and

1.72-1.20 (m, 6, $\underline{CH_3}CHBr$ and $\underline{CH_3}CHF$);

^{19}F nmr multiplet at -5.2 and heptet at -8.96.

1.4 Preparation of 1-fluoro-2-methylpropane

The procedure was identical with that mentioned above and the product without isolation was identified by means of nmr spectrum.

^{1}H nmr δ 2.3-1.9 (m, 3, $(CH_3)_2\underline{CH}-\underline{CH_2}F$) and 1.3 (d, 6, $\underline{CH_3}-CH-\underline{CH_3}$).

1.5 C-alkylation of ethyl acetoacetate with 2-bromo-3-fluorobutane (2)

1.5.1 To 50 ml of diglyme, 0.68 g (0.01 mole) of pulverized ethanol-free

sodium ethoxide was added. The resulting mixture was stirred vigorously, and then 0.5 g of sodium iodide was added followed by the addition of an equimolar amount (1.3 g = (0.01 mole) of ethyl acetoacetate. To the resulting mixture, 1.55 g (0.01 mole) of 2 was added all at once, and the mixture was stirred at 100° for 4 hr and then partitioned between ether and water. The ethereal layer was dried and concentrated to leave only the starting materials.

1.52 To 0.24 g (0.01 mole) of sodium hydride in 50 ml of diglyme, an equimolar amount of ethyl acetoacetate was added, and the resulting mixture was stirred until ethyl sodioacetoacetate was formed. To that mixture, 1.55 g (0.01 mole) of 2 was added followed by the addition of an equimolar amount of sodium iodide. The mixture was stirred at 110° for 4 hr and worked up in the same fashion as mentioned above. The organic layer contained no fluorine (as checked by fluorine nmr spectrum), and fluoride ion was found in the aqueous layer.

1.53 The same results were obtained when the reaction was carried out in tetramethylene sulfone at 110°, or in dimethylformamide at 120°.

1.6 C-alkylation of diethyl acetamidomalonate with 2

1.61 The procedure was analogous to 1.5.2 and 1.5.3, with ethylene glycol dimethyl ether as the solvent and diethyl acetamidomalonate-sodium salt as the nucleophile. The mixture was stirred and refluxed for 24 hr and worked up as before. Only the starting material was obtained.

1.6.1 To 0.24 g (0.01 mole) of sodium hydride (99 per cent pure, from PCR) in 50 ml of benzene, 2.17 (0.01 mole) of diethyl acetamidomalonate was added, and the resulting mixture was refluxed until no more sodium salt was formed, as followed by the evolution of H_2. The solvent was removed under a vacuum, the diethyl sodioacetamidomalonate was transferred into a glass ampul, 15.5 g (0.1 mole) of 2-bromo-3-fluorobutane (2) was added, and the ampul was sealed. After heating at 80° for 4 hr, only the starting material was recovered.

After heating at 120° for the same period of time, fluoride ion was found in the aqueous layer.

1.7 C-alkylation of cyclopentadiene with 2-bromo-3-fluorobutane[76]

To 3.83 g (0.091 mole) of sodium hydride (57 per cent dispersion in paraffin oil) in 150 ml of diethylene glycol dimethyl ether, 6 g (0.091 mole) of cyclopentadiene was added, and the mixture was heated for 1 hr at 69°. To the resulting sodium salt of cyclopentadien, 13.75 (0.091 mole) of 3-bromo-2-butanone was added, and mixture was stirred at 69° for 6 hr (during that time pH changed from strongly basic to 7). The resulting mixture was partitioned between ether and water; the ethereal layer was dried and concentrated, but all attempts to distill the resulting oil ended by an extensive polymerization.

1.8 Preparation of ethyl 2-ethoxycarbonyl-4-keto-3-methylpentanoate

To 1.59 g (0.0378 mole) of sodium hydride (57% dispersion in paraffin oil) in 100 ml of ether, 8.65 ml (0.057 mole) of diethylmalonate

was added dropwise, and mixture was refluxed for two hours with vigorous stirring. To the resulting vixcous mixture, 5.7 g (0.0378 mole) of 3-bromo-2-butanone was added, and the mixture was stirred and refluxed overnight. The product was obtained in 60 per cent yield (5.2 g): bp 70-74° (0.02 mm).

2.1 Preparation of benzyl chloroacetate

To 100 g (0.885 mole) of chloroacetyl chloride, a mixture of 95.6 g (0.885 mole) of benzyl alcohol and 72 ml (0.885 mole) of pyridine was added dropwise with vigorous stirring so that the temperature of the resulting mixture did not exceed 20°. The resulting thick mixture was then stirred at 90° for 2 hr, partitioned between water and ether, and the ethereal layer was washed with sulfuric acid (10 per cent), water, aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Concentration of the ethereal layer yielded 142 g (87 per cent) of benzyl chloroacetate: bp 79-81° (0.01 mm).

^{1}H nmr δ 7.25 (s,5,PhCH_2-), 5.05 (s,2,-COOCH_2Ph), and 3.9 (s,2,ClCH_2COO-);

2.2 Preparation of tert-butyl chloroacetate

In the manner described above, a solution of 75.5 ml (0.8 mole) of tert-butyl alcohol and 100 ml (0.8 mole) of N,N-dimethylaniline was added to 100 g (0.8 mole) of chloroacetyl chloride; 66.5 g (55 per cent) of a colorless liquid was obtained: bp 58-59° (18 mm).

^{1}H nmr δ 3.9 (s,2,ClCH_2COO-) and 1.5 (s,9,-COOC(CH_3)$_3$);

2.3 Preparation of methyl diethylphosphonoacetate by means of Arbuzov rearrangement (25a)[20]

To 108.53 g (1 mole) of methyl chloroacetate, one third of 166.17 g (1 mole) of triethyl phosphite was added, and the mixture was vigorously stirred while heated with a free flame. In a few minutes,

the mixture was brought to boiling, and at the same time intensive evolution of ethyl chloride started. The rest of the triethyl phosphite was added at such a rate that the mixture was boiling without external heating. After the equimolar amount of triethyl phosphite had been added, the resulting mixture was stirred at 140° for 2 hr, cooled, and distilled through a 20 cm column. Methyl diethylphosphonoacetate (25a) was obtained in 76 per cent yield (159.5 g): bp 85-87° (0.005 mm).

^{1}H nmr δ 4.1 (quint.,4,$CH_3\underline{CH_2}O)_2P$), 3.62 (s,3,$COO\underline{CH_3}$),
2.9 ($d_{J=22Hz}$,2, P-$\underline{CH_2}$-), and
1.3 (t,6,$\underline{CH_3}CH_2O)_2P$)

2.4 Preparation of ethyl diethylphosphonoacetate (25b)

In the manner described in 2.3, 440 ml (2.04 mole) of triethylphosphite was added to 250 g (2.04 mole) of ethyl chloroacetate to give 430.5 g (94 per cent) of 25b: bp 146-148° (10 mm).

^{1}H nmr δ 4.0 (quint.,6,$CH_3\underline{CH_2}O)_2P$ and $COO\underline{CH_2}CH_3$),
2.95 ($d_{J=22}$,P-$\underline{CH_2}$-), and 1.2 (t,9,$\underline{CH_3}CH_2O)_2P$
and $\underline{CH_3}CH_2OOC$-);

2.5 Preparation of tert-butyl diethylphosphonoacetate (25c)

In the manner described in 2.3 the title compound was prepared in 74 per cent yield, bp 90-94° (0.02 mm).

^{1}H nmr δ 4.1 (quint.,4,$CH_3\underline{CH_2}O)_2P$-), 2.9 ($d_{J=22}$,2,$P\underline{CH_2}$),
1.45 (s,9,-$COOC(\underline{CH_3})_3$), and 1.3 (t,6,$\underline{CH_3}CH_2O)_2P$);

2.6 Preparation of benzyl diethylphosphonoacetate (25d)

In the manner described in 2.3, 62.3 ml (0.3 mole) of triethylphosphite was added to 46 ml (0.3 mole) of benzyl chloroacetate and 69 g (78 per cent) of 25d was obtained, bp 140-144 (0.02 mm).

^{1}H nmr δ 7.3 (s,5,$\underline{Ph}CH_2$), 5.08 (s,2,-COO$\underline{CH_2}$Ph),
4.0 (quint.,4,$CH_3\underline{CH_2}O)_2P$),
2.95 ($d_{J=22Hz}$,2,-P-$\underline{CH_2}$-), and 1.2 (t,6,$\underline{CH_3}CH_2O)_2P$);

2.7 Preparation of 3-chloro-2-butanone (26)[21]

Into 500 g (6.94 mole) of 2-butanone, 400 g (5.64 mole) of chlorine was bubbled at 8° (ice-water bath) for 12 hr, the resulting yellow solution was washed with water four times and dried over calcium chloride. Distillation through a 50 cm column filled with glass beads, using a reflux ratio of 1:5, gave 364 g (58 per cent) of 26, bp 54-60° (80 mm);

^{1}H nmr δ 4.5 (quart.,1,$\underline{CH}$Cl), 2.3 (s,3,$\underline{CH_3}$CO-), and
1.58 (d,3,CHCl$\underline{CH_3}$);

Also, 50 g (8 per cent) of 1-chloro-2-butanone was obtained, bp 72-80° (70 mm);

^{1}H mnr δ 4.32 (s,2,Cl$\underline{CH_2}$CO), 2.65 (quart.,2,-$\underline{CH_2}CH_3$), and
1.05 (t,3,-$CH_2\underline{CH_3}$).

2.8 Preparation of 3-bromo-2-butanone (10)[28]

To a mixture of 32.4 ml (0.36 mole) of 2-butanone, 5.52 g (0.045 mole) of potassium chlorate, and 24 ml of water, a few drops of bromine was added and the temperature of the reaction mixture was brought to 58° at which temperature decolorization started. The rest of the bromine (0.2 mole) was added portionwise so that the temperature did not drop below 58° (if the temperature rises too fast a cold water bath must be applied to prevent the temperature from rising above 85°). In this manner even large amounts of bromine could be added within a short period of time (e.g. 210 ml of bromine within 1 hr).

The resulting mixture was washed three times with water, dried over calcium chloride and distilled through a 30 cm column. The product was obtained in 75 per cent yield, bp 67-69° (63 mm).

^{1}H nmr δ 4.3 (quart.,1,$\underline{\text{CH}}$Br), 2.3 (s,3,$\underline{\text{CH}_3}$CO), and

1.7 (d,3,CHBr$\underline{\text{CH}_3}$).

The product, 3-bromo-2-butanone, was contaminated with 10 per cent of 1-bromo-2-butanone.

2.9 Preparation of 3-fluoro-2-butanone (17)[22]

2.91 To a mixture of 900 ml of diethylene glycol and 316 g (5.45 mole) of potassium fluoride (dried for 2 hr at 110°) vigorously stirred at 180°, 364 g (3.29 mole) of 3-chloro-2-butanone was added dropwise. The product was distilled off through a column simultaneously, bp 69-78° (760 mm), dried over magnesium sulfate, and redistilled through a 30 cm

column giving 3-fluoro-2-butanone in 60 per cent yield (177 g), bp 74-75° (760 mm):

^{1}H nmr δ 4.7 (pair of quart., $_{J=48Hz}$,1,$\underline{CH}FCH_3$),

2.05 ($d_{J=5Hz}$,3,$\underline{CH_3}CO$), and

1.32 (pair of $d_{J=24Hz}$,3,$CHF\underline{CH_3}$);

^{19}F nmr sextet at -18.8 with J_{gem}50Hz,J_{vic}25Hz.

Each line of the sextet, expanded to 540 Hz is split into quartet with J=5Hz (see Figure 1).

2.92 Using 3-bromo-2-butanone as a starting material, 3-fluoro-2-butanone was obtained in 55 per cent yield, in the manner described in 2.9.1.

2.10 Attempts to prepare 3-fluoro-2-butanone from 3-hydroxy-2-butanone as a starting material

2.10.1 To 27 g (0.307 mole) of 3-hydroxy-2-butanone in 100 ml of methylene chloride, 66.3 g (0.35 mole) of 2-chloro-1,1,2-trifluoro-triethylamine was added and the mixture was stirred at room temperature for 12 hr. The resulting solution was washed three times with water, once with aqueous sodium bicarbonate, and dried over magnesium sulfate. The product was a mixture of several compounds which could not be separated or identified.

2.10.2 To 22 g (0.25 mole) of acetoin in 80.5 ml (1 mole) of pyridine, 52.5 g (0.275 mole) of p-toluenesulfonyl chloride was added with vigorous

stirring at 15°. The mixture was stirred for 3 hr at 20°, then poured into ice-water, acidified with dilute hydrochloric acid, and extracted with methylene chloride. Most of the starting material was recovered, and only traces of the product (26) were obtained, bp 117-120° (0.005 mm). The only proof of the structure was the disappearance of the hydroxyl band at 3500 cm^{-1} in the infra red spectrum.

2.10.3 To 19.7 g (0.223 mole) of acetoin in 35 ml (0.275 mole) of N,N-dimethylaniline, 25.7 g (0.237 mole) of chlorotrimethylsilane was added; two layers were formed, and the upper one was separated. Distillation gave 11 g (30 per cent) of 3-trimethylsilyloxy-2-butanone, bp 145-152° (760 mm). The ir spectra indicated the formation of trimethylsilyl ether.

2.11 Preparation of phenyltetrafluorophosphorane[24]

To 134 g (0.75 mole) of phenyldichlorophosphine, 197 g (1.1 mole) of antimony trifluoride was added with vigorous stirring at 40° so that the temperature did not exceed 50°. The resulting mixture was stirred at 60° for another hour, and the product was obtained in 60 per cent yield, bp 70-71° (70 mm).

2.12 Reaction between 3-O-trimethylsilyl-2-butanone and phenyltetrafluorophosphorane

To 11 g (0.0687 mole) of the trimethylsilyl ether, 13.3 g (0.072 mole) of phenyltetrafluorophosphorane was added dropwise in a nitrogen atmosphere at 8° to give a dark solution. Severe decomposition

occurred during the attempted distillation.

2.13 Reaction between 3-hydroxy-2-butanone and thionylchloride[25]

To 2.9 g (0.033 mole) of acetoin and 3 ml (0.035 mole) of pyridine in 15 ml of benzene, 2.5 ml (0.035 mole) of thionyl chloride in 10 ml of benzene was added, and the mixture was stirred and refluxed for 4 hr. The resulting dark liquid was washed with aqueous sodium bicarbonate and dried over magnesium sulfate. Distillation gave a mixture of several compounds, and no pure product was isolated.

2.14 Reaction between acetoin and phosphorus tribromide[27]

To a solution of acetoin in benzene an equimolar amount of phosphorus tribromide was added at -10° under nitrogen, which resulted in formation of an inseparable mixture of several compounds.

2.15 Preparation of 3-chloro-2-butanone from 2-butanone and copper II chloride[23]

To a mixture of 122 g (0.72 mole) of copper (II) chloridedihydrate and 30.5 g (0.72 mole) of lithium chloride in 360 ml of dimethylformamide, 510 ml (0.6 mole) of 2-butanone was added with stirring at 80°. After 1 hr, the resulting mixture was diluted with 90 g of ice and extracted with pentane; the pentane layer was dried, and 3-chloro-2-butanone was obtained in 22 per cent yield. For the proton nmr data see 2.7.

CONDENSATION OF DIETHYLPHOSPHONOACETATES WITH 3-FLUORO-2-BUTANONE

2.16 Preparation of methyl 4-fluoro-3-methyl-2-pentenoate (19a)[14]

To a suspension of 2.7 g (0.0645 mole) of sodium hydride in 100 ml of ether, 13.5 g (0.0643 mole) of methyl diethylphosphonoacetate was added with vigorous stirring at 8° (ice-water bath). A clear solution resulted to which 5.8 g (0.064 mole) of 3-fluoro-2-butanone (17) was added dropwise. A thick oil separated in a few minutes (which indicated termination of the condensation), the mixture was stirred at room temperature for an additional half hour, water was added, and the ether layer was separated and dried. Distillation gave 51 g (64 per cent) of 19a, bp 58-62° (12 mm), a mixture of Z and E form.

^{1}H nmr δ5.75 and 5.58 (s,1,=CH-),

4.9 (pair of quart.$_{J=50Hz}$,1,CHF),

3.6 (s,3,$\underline{CH_3}$OOC-), 2.03 and 1.88 (s,3,$\underline{CH_3}$C=), and

1.39 (pair of d$_{J=25Hz}$,3,CHF$\underline{CH_3}$);

The ratio of two vinylic protons E:Z=75:25, the ratio of methyl protons E:Z=77:23.

^{19}F nmr sextet at -10.09 (E) with J_{gem}=50Hz,J_{vic}=25Hz, and

sextet at -16.13 (Z) with the same J's as above.

The ratio E:Z=74:26.

Pure E-form (concluded from the chemical shift) was isolated by distillation through a 20 cm column, bp 82-84° (28 mm);

^{1}H nmr δ 5.75 (s,1,=CH-), 4.9 (pair of quart.,1,CHF),
3.6 (s,3,-COOCH$_3$), 2.03 (s,3,=C-CH$_3$), and
1.39 (pair of d$_{J=25Hz}$,3,CHFCH$_3$);

^{19}F nmr sextet at -10.09 with J_{gem}=50 and J_{vic}=25Hz.

2.17 Preparation of ethyl 4-fluoro-3-methyl-2-pentenoate (19b)

In the manner described in 2.16, the title compound was prepared in 76 per cent yield starting from 4.7 g (0.0522 mole) of 17, 11.7 g (0.0522 mole) of ethyl diethylphosphonoacetate, and 2.2 g (0.0522 mole) of sodium hydride. The product had bp 72-75° (8 mm):

^{1}H nmr δ 6.5 and 5.3 (two pairs of quart.$_{J=50Hz}$,1,CHF),
6.15 and 5.95 (s,1,=CH-), 4.5 (quart.,2,-COOCH$_2$CH$_3$),
2.5 and 2.4 (s,3,=CCH$_3$), and
2.05-1.65 (m,6,CHFCH$_3$ and -COOCH$_2$CH$_3$):

The ratio of two vinylic protons E:Z=74:26, and the ratio of methyl protons E:Z=78:22.

^{19}F nmr sextet at -11.03 (E) with J_{gem}=50 and J_{vic}=25Hz and
sextet at -17.47 (Z) with the same J's as above. The ratio of E:Z=75:25.

2.18 Preparation of tert-butyl 4-fluoro-3-methyl-2-pentenoate (19c)

The product was obtained in the same manner as described above

in 64.5 per cent yield, bp 40-44° (0.05 mm):

^{1}H nmr δ 5.75 and 5.6 (s,1,=CH), 4.9 (pair of quart.$_{J=50Hz}$,1,$\underline{CH}FCH_3$), 2.05 and 1.95 (s,3,=C$\underline{CH_3}$), and 1.6-1.2 (m,12,CHF$\underline{CH_3}$ and -COOC($\underline{CH_3}$)$_3$);

Ratio of methyl protons E:Z=76:24.

^{19}F nmr sextet at -11 (E) with J_{gem}=50 and J_{vic}=25Hz and sextet at -17 (Z) with same J's as above, with ratio E:Z=75:25.

2.19 Preparation of benzyl 4-fluoro-3-methyl-2-pentenoate (19d)

In the manner described above, 19d was prepared in 80 per cent yield, bp 104-105° (0.02 mm).

^{1}H nmr δ 7.32 (s,5,Ph), 5.95 and 5.7 (s,1,=CH),
5.05 (s,2,-$\underline{CH_2}$Ph),
4.95 (pair of quart.$_{J=50Hz}$,1,$\underline{CH}FCH_3$),
2.05 and 1.95 (s,3,$\underline{CH_3}$C=), and
1.35 (pair of d$_{J=25Hz}$,3,CHF$\underline{CH_3}$):

The ratio of vinylic protons E:Z=76:24, and the ratio of methyl protons E:Z=75:25.

^{19}F nmr sextet at -10.74 and sextet at -17.3 with E:Z=75:25 and with J_{gem}=50 and J_{vic}=25Hz.

CATALYTIC HYDROGENATION OF METHYL-, ETHYL-, TERT-BUTYL- AND BENZYL ESTERS OF 4-FLUORO-3-METHYL-2-PENTENOATE

2.20 Preparation of methyl 4-fluoro-3-methyl-pentanoate (20a)

Hydrogenation of 18.5 g (0.127 mole) of 19a dissolved in 250 ml of ether over 7 g of rhodium on carbon under 4 atm of hydrogen in an apparatus described in the Appendix gave 16 g (85 per cent yield) of 20a, bp 31-34° (0.05 mm).

^{1}H nmr δ 4.5 (pair of $m_{J=50Hz}$,1,CHF), 3.6 (s,3,$COOCH_3$),
2.7-1.7 (m,3,$CH_3\underline{CH}-\underline{CH_2}-COO-$),
1.25 (pair of $d_{J=25Hz}$,3,$CHF\underline{CH_3}$), and 0.9 (d,3,$\underline{CH_3}CH-$);

^{19}F nmr multiplet at -13.13 and heptet at -19.7.

2.21 Preparation of ethyl 4-fluoro-3-methyl-pentanoate (20b)

In the manner described above, 20b was obtained in 85 per cent yield, bp 72-76° (20 mm) and 31-34° (0.1 mm).

^{1}H nmr δ 4.8-3.95 (m,3,CHF and $-COO\underline{CH_2}CH_3$),
2.6-1.7 (m,3,$CH_3\underline{CH}-\underline{CH_2}-COO-$),
1.7-1.05 (m,6,$CHF\underline{CH_3}$ and $COOCH_2\underline{CH_3}$), and 0.95 (d,3,$\underline{CH_3}CH-$);

^{19}F nmr multiplet at -14.0 and heptet at -20.7.

2.22 Preparation of tert-butyl 4-fluoro-3-methyl-pentanoate (20c)

In the manner described in 2.20, the title compound was obtained

in 95 per cent yield, bp 34-38° (0.15 mm).

^{1}H nmr δ 4.65 (pair of $m_{J=50Hz}$,1,CHF),

2.8-1.8 (m,3,-CH-CH_2-COO-) and

1.65-0.98 (m,15,CH_3CH-,CH_3CHF-, and -COOC(CH_3)$_3$).

^{19}F nmr multiplet at -13.43 and heptet at -19.7.

2.23 Preparation of 4-fluoro-3-methyl-pentanoic acid (21)

Hydrogenation of 19d in ether over rhodium on carbon in the manner described above afforded 21 in 65 per cent yield, bp 54-60° (0.025 mm).

^{1}H nmr δ 12.35 (s,1,-COOH), 4.05 (d of $m_{J=50Hz}$,1,CHF),

2.4-1.7 (m,3,-CH-CH_2-COOH), and

1.1-0.8 (m,6,CH_3CH and CHFCH_3).

^{19}F nmr multiplet at -14.33 and heptet at -21.79.

2.24 Attempts to prepare benzyl 2-bromo-4-fluoro-3-methylpentanoate (22d)

2.24.1 To a vigorously stirred mixture of 1.14 g (0.0085 mole) of 21 and 0.85 ml (0.0089 mole) of phosphorus tribromide, 1 ml of bromine was added at 100° in two portions. The mixture was stirred on a steam bath for 4 hr, cooled, and 8 equivalents of benzyl alcohol were added. After 30 min stirring at room temperature the mixture was heated at 80° for 1 hr, cooled again, partitioned between ether and water, the ethereal layer was washed with a solution of sodium bicarbonate and dried. The resulting oil did not contain fluorine.

The same experiment was performed at temperatures between 80-100° but with the same results as above.

2.24.2 To 3.7 g (0.0276 mole) of 21, 2.6 ml (0.035 mole) of thionyl chloride was added and the mixture was refluxed for 1 hr. The unreacted thionyl chloride was evaporated under vacuum, 25 ml of carbon tetrachloride was added followed by 6.23 g (0.035 mole) of NBS. The mixture was refluxed for 1.5 hr, succinimide was filtered off, and the solvent was evaporated. The resulting oil contained no fluorine.

2.25 Preparation of ethyl 2,3-dibromo-4-fluoro-3-methylpentanoate (27)

To 13.1 g (0.082 mole) of 19b in 50 ml of carbon tetrachloride, 5 ml (0.094 mole) of bromine was added dropwise at 4° and the mixture was kept at room temperature for 4 days. It was then washed with water, aqueous sodium bicarbonate, and dried over magnesium sulfate. The title compound was prepared in 95 per cent yield (25 g), bp 60-64° (0.015 mm).

^{1}H nmr δ 4.9-3.9 (m,4,CHF,-CH(Br)-COOCH$_2$CH$_3$),

2.08 and 1.95 (s,3,CH$_3$CHBr), and

1.75-1.05 (m,6,CH$_3$CHF and COOCH$_2$CH$_3$).

^{19}F nmr sextet at -7.76,

multiplet and sextet overlap at -9.57, and sextet at -14.36.

2.26 Preparation of ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate (28)

Dehydrobromination of 27 was achieved by refluxing the mixture of

4 g (0.048 mole) of sodium acetate and 14 g (0.044 mole) of 27 in 35 ml of ethanol for 4½ hr. The solvent was removed under vacuum, the residue was partitioned between ether and water, the ethereal layer was washed with a solution of sodium bicarbonate, and dried. The product (28) was obtained in 80 per cent yield (8.4 g), bp 39-40° (0.01 mm);

^{1}H nmr δ 6.05 (pair of quart.$_{J=50Hz}$,1,CHF),

4.55 (quart.,2,-COO$\underline{CH_2}CH_3$),

2.39 (d$_{J=3Hz}$,3,CH_3C=), and

2.05-1.5 (m,6,$\underline{CH_3}$CHF and -COO$CH_2\underline{CH_3}$); Ratio of two vinyl protons E:Z=60:40.

^{19}F nmr sextet at -10.64 and sextet at -17.02.

2.27 Attempts to reduce ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate

8.4 g (0.035 mole) of 28 was dissolved in 70 ml of ether, and 2 g of rhodium on aluminum oxide was added. The pressure of hydrogen was increased from 1-55 atm but no uptake of hydrogen was observed even after two days. When the pressure was increased over 60 atm, a cleavage of carbon-fluorine bond was observed.

3.1 Preparation of ethyl 1,1-dichloro-1-diethylphosphonoacetate (32)[40]

Chlorine gas was introduced into a mixture of 112.1 g (0.5 mole) of ethyl diethylphosphonoacetate and 50 g (0.5 mole) of calcium carbonate at 0-5° until all the carbonate reacted. The mixture was extracted with chloroform, and the organic layer was washed with solutions of sodium bisulfite, sodium bicarbonate, and a saturated solution of sodium chloride. Distillation gave 126.3 g (86 per cent) of 32, bp 87-88° (0.015 mm);

^{1}H nmr δ 4.45 (quint.,6,$CH_3\underline{CH_2}O)_2PCCl_2CO_2\underline{CH_2}CH_3$), and

1.5 (t,9,$\underline{CH_3}CH_2O)_2PCCl_2COOCH_2\underline{CH_3}$).

3.2 Preparation of ethyl 1-chloro-1-diethylphosphonoacetate (30)[40]

To a suspension of 10.5 g (0.227 mole) of sodium hydride (57% dispersion in paraffin oil) in 500 ml of benzene, 51 g (0.2274 mole) of ethyl diethylphosphonoacetate was added at 4°, the resulting solution was warmed to room temperature, and 66.65 g (0.227 mole) of 32 was added. The reaction mixture was stirred at 22° for 4 hr, quenched with water, and the benzene layer was separated.

Three consecutive distillations of the resulting oil through a 30 cm column gave 30 per cent yield of 30, bp 99-102° (0.15 mm);

^{1}H nmr δ 4.7 ($d_{J=18Hz}$,1,P-CHCl-), 4.5-4.0 (m,6,$CH_3\underline{CH_2}O)_2P$ and $-COO\underline{CH_2}CH_3$),

and 1.5-1.2 (m,9,$\underline{CH_3}CH_2O)_2P$ and -C))$CH_2\underline{CH_3}$).

3.3 Preparation of ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate (29)[40]

To 2.77 g (0.066 mole) of sodium hydride (57% dispersion in paraffin oil) in 100 ml of ether, 17 g (0.066 mole) of 30 was added, and the mixture was stirred for ½ hr at room temperature. To the resulting solution, 5.9 g (0.066 mole) of 3-fluoro-2-butanone was added, the mixture was refluxed for 2 hr, and quenched with water. The ethereal layer was dried over magnesium sulfate, the ether was removed under vacuum, and the product was obtained in 63 per cent yield, bp 42-45° (0.02 mm).

^{1}H nmr δ 6.0 (pair of quart.$_{J=50Hz}$,1,CHF), 4.2 (quart.,2,COO$\underline{CH_2}CH_3$),
2.1 and 2.0 (d,3,CH_3C=), and
1.6-1.1 (m,6,$\underline{CH_3}CHF$ and $COOCH_2\underline{CH_3}$);

^{19}F nmr sextets at -11.5 and -18.

3.4 Preparation of ethyl 3-methyl-2-pentenoate

This compound was prepared in 70 percent yield from 2-butanone and ethyl diethylphosphonoacetate in a manner described earlier (2.16), bp 49-52° (10 mm);

^{1}H nmr δ 6.0 (s,1,=CH), 4.5 (quart.,2,-COO$\underline{CH_2}CH_3$),
2.4 (s,3,CH_3C=), and 1.5 (m,6,$\underline{CH_3}CH_2C$= and $COOCH_2\underline{CH_3}$).

3.5 Preparation of ethyl 3-methyl-2-nitro-2-pentenoate

To 19 ml of 82 per cent nitric acid, 7.0 g (0.048 mole) of ethyl 3-methyl-2-pentenoate was added dropwise at 17-19°, and the mixture

was stirred at 30° for six hours. The mixture was poured onto ice, extracted with ether, and the ether extract was dried over magnesium sulfate. Distillation gave 2.8 g (30 per cent yield) of a product, bp 122-125°(12 mm).

^{1}H nmr δ 4.5 (quart.,2,-COO$\underline{CH_2}CH_3$), 2.9 (quart.,2,$CH_3\underline{CH_2}C$=),

2.5 and 2.2 (s,3,CH_3C=) and

1.5 (m,6,$\underline{CH_3}CH_2C$= and -COO$CH_2\underline{CH_3}$).

3.6 Attempt to prepare ethyl 4-fluoro-3-methyl-2-nitro-2-pentenoate

Ethyl 4-fluoro-3-methyl-2-pentenoate was added to 82 per cent nitric acid in the same manner as described above but the resulting product was fluorine-free.

3.7 Attempts to prepare benzyl 4-fluoro-3-methyl-2-aminopentanoate

To a suspension of 0.153 g (0.004 mole) of sodium borohydride in 20 ml of ethylene glycol dimethyl ether, 0.77 g (0.005 mole of boron trifluoride-ether complex was added followed by the addition of 2.22 g (0.01 mole) of 19d in 10 ml of the same solvent. After stirring the mixture at room temperature for 2 hr, 1.35 g (0.012 mole) of hydroxylamine-O-sulfonic acid was added the mixture was vigorously stirred at 100° for 1½ hr, then quenched with water, and the water layer was extracted with ether. Concentration of the solution gave an oil which was free of fluorine.

4.1 Preparation of diethyl bromomalonate (34)[50]

The title compound was prepared in 70 per cent yield, from diethyl malonate and bromine in carbon tetrachloride; bp 79-80° (0.03 mm)

^{1}H nmr δ 4.75 (s,1,CHBr), 4.25 (quart.,4,-C))$\underline{CH_2}CH_3$), and 1.35 (t,6,-COOCH$_2\underline{CH_3}$).

4.2 Preparation of diethyl diethylphosphonomalonate (35)[51]

To 7.8 g (0.033 mole) of diethyl bromomalonate, 3.5 ml of triethylphosphite was added dropwise so that the mixture refluxed moderately. After the all triethylphosphite was added, the mixture was stirred on a steam bath for 3 hr, and the product was obtained in 95 per cent yield (9.3g), bp 137-139° (0.03 mm).

^{1}H nmr δ 4.25 (m,9,$CH_3\underline{CH_2}O)_2P\underline{CH}(COO\underline{CH_2}CH_3)_2$) and 1.4 (m,12,$\underline{CH_3}CH_2O)_2PCH(COOCH_2\underline{CH_3})_2$).

4.3 Preparation of ethyl α-chloroacetoacetate (37)[53]

To 51 ml (0.4 mole) of ethylacetoacetate, an equimolar amount of sulfuryl chloride was added dropwise at 30-40°, and the resulting dark mixture was distilled through a 15 cm column. The product was obtained in 60 per cent yield (39.5 g), bp 48-51° (0.07 mm).

^{1}H nmr δ 6.0 (s,1,CHCl), 4.3 (quart.,2,COO$\underline{CH_2}CH_3$), 2.35 (s,3,CH_3CO), and 1.3 (t,3,-C))$CH_2\underline{CH_3}$).

4.4 Preparation of ethyl α-chloroacetoacetate ethyleneketal

To 41 g (0.25 mole) of 37 in 500 ml of benzene, 30 ml of ethylene glycol and 0.2 g of p-toluenesulfonic acid were added, and the mixture was heated under reflux for 4 hr while water was collected in a Dean-Starck apparatus. The reaction mixture was cooled and the benzene was evaporated under vacuum. The remaining liquid was distilled to give 23.3 g (45 per cent) of the product, bp 67-69° (0.025 mm);

^{1}H nmr δ 4.3-3.9 (m,7,-O$\underline{CH_2CH_2}$O-,CHCl, and -COO$\underline{CH_2}CH_3$)

1.5 (s,3,CH_3C (ketal)), and

1.3 (t,3,-COOCH$_2\underline{CH_3}$).

4.5 Preparation of diethyl oxomalonate (39)[55]

The title compound, bp 76-80° (0.025 mm), was prepared in 40 per cent yield from diethyl malonate and nitrogen- (III) oxide (prepared from concentrated nitric acid and arsenous oxide) at -15° for 6 hr.

^{1}H nmr δ 4.3 (quart.,4,-COO$\underline{CH_2}CH_3$) and

1.3 (t,6,-COOCH$_2\underline{CH_3}$).

4.6 Attempt to prepare 3-fluoro-2-butylidene triphenylphosphorane (38)

3.6 g(0.023 mole) of 2-bromo-3-fluorobutane and 6.55 g (0.025 mole) of triphenylphosphine was refluxed in 25 ml of benzene for 24 hr but only the starting material was recovered. When the mixture of triphenylphosphine and 2-bromo-3-fluorobutane was sealed in a glass ampul and heated at 115° for 4 hr, fluorine was eliminated.

5.1 Preparation of methyl dimethoxyacetate (46)[56]

To 1.5l of 4.7 M solution of sodium methoxide in methanol, 258 g (2 mole) of dichloroacetic acid was added at 8° and the solution was refluxed for 5 hr. The resulting mixture was neutralized with a solution of hydrogen chloride in methanol (phenolphtalein was the indicator), and 72 ml (1 mole) of thionyl chloride was added at 10-25°. After stirring overnight the reaction mixture was concentrated and the product distilled to give 150 g (46 per cent) of 46, bp 66-68° (18 mm).

^{1}H nmr δ 4.7 (s,1,=CH), 3.62 (s,3,-COOCH$_3$), and
3.24 (s,6,CH$_3$O)$_2$CH).

5.2 Preparation of methyl methoxychloroacetate (47)[56]

To 60 g (0.287 mole) of phosphorus pentachloride, 38.45 g (0.287 mole) of 46 was added dropwise, the solution was refluxed for an additional ½ hr and distilled through a 30 cm column to give 30 g (75 per cent) of 47, bp 63-68 (11 mm);

^{1}H nmr δ 5.8 (s,1,CHCl), 3.8 (s,3,CH$_3$OOC-), and
3.6 (s,3,CH$_3$OCHCl).

5.3 Preparation of methyl methoxypiperidinoacetate (48)[58]

To 13.85 g (0.1 mole) of 47 in 250 ml of ether, 17.0 g (0.2 mole) of piperidine was added dropwise at -12°. The precipitate was filtered off, and the ether layer was washed with water. Ether was removed

under reduced pressure, and the product was obtained in 65 per cent yield (12.2 g), bp 68-70° (0.02 mm)

^{1}H nmr δ 4.0 (s,1,CH), 3.6 (s,3,-COOC$\underline{H_3}$), 3.2 (s,3,$\underline{CH_3}$OCH), and 2.6-2.5 and 1.5-1.4 (m,10, N(CH_2)$_5$).

5.4 Preparation of tert-butyl methoxyacetate (49)[62]

100 g (0.556 mole) of methoxyacetic acid was placed in an autoclave and 250 ml of 2-methylpropene was condensed in it at -78° (Dry Ice-acetone bath) followed by the addition of 3 ml of concentrated sulfuric acid. The autoclave was sealed, shaken at room temperature overnight, the mixture was poured into a 10 per cent sodium hydroxide, and extracted with ether. Distillation afforded 60 g (74 per cent yield) of 49, bp 59-61° (20 mm)

^{1}H nmr δ 3.95 (s,2,CH_2), 3.55 (s,3,$\underline{CH_3}$OCH_2-), and 1.65 (s,9,-COOC($\underline{CH_3}$)$_3$).

5.5 Preparation of tert-butyl methoxybromoacetate (50)[62]

To 33.6 g (0.23 mole) of 49 in 250 ml of carbon tetrachloride containing a few crystals of benzoyl peroxide, 22.0 g (0.23 mole) of N-bromosuccinimide was added, and mixture was refluxed for 1 hr. The deposited succinimide was filtered off, and the solvent was removed under reduced pressure. Distillation gave 39 g (78 per cent yield) of 50, bp 49-53° (0.02 mm)

^{1}H nmr δ 5.8 (s,1,CHBr), 3.42 (s,3,CH_3O, and 1.4 (s,9,-COOC($\underline{CH_3}$)$_3$).

5.6 Preparation of tert-butyl methoxy-N,N-dibenzylaminoacetate (51)

A mixture of 15.5 ml (0.08 mole) of dibenzylamine and 11.2 ml (0.08 mole) of triethylamine in 30 ml of ether was added dropwise to 18.0g (0.08 mole) of 50 in 250 ml of ether at -78° (Dry Ice-acetone). The mixture was stirred at the same temperature for 2 hr, the precipitated salt was filtered off the ethereal layer was washed three times with water, and dried over magnesium sulfate.

The solvent was removed under reduced pressure giving a thick oil which could not be distilled or crystallized.

^{1}H nmr δ 7.1 (m,10,Ph), 3.95 (s,1,CH), 3.65 (s,4,Ph$\underline{CH_2}$N), 3.15 (s,3,$\underline{CH_3}$OCH), and 1.4 (s,9,-COOC(CH_3)$_3$).

5.7 Preparation of benzyl dichloroacetate

The title compound was prepared in 70 per cent yield from dichloroacetyl chloride and an equimolar amount of benzyl alcohol and pyridine in the same manner as described earlier (see 2.1). Benzyl dichloroacetate has bp 88-91° (0.05 mm)

^{1}H nmr δ 7.35 (s,5,Ph), 6.0 (s,1,$CHCl_2$) and 5.15 (s,2,-COOCH_2Ph).

5.8 Preparation of tert-butyl methoxydiethylphosphonoacetate (52)

To 17 g (0.0755 mole) of tert-butyl methoxybromoacetate, an equimolar amount of triethyl phosphite was added dropwise, the mixture was heated at 140° for ½ hr, and distilled to give 18 g (85 per cent yield) of the product, bp 103-108° (0.025 mm);

^{1}H nmr δ 4.1-3.7 (m,5,$CH_3\underline{CH_2}O)_2P\underline{CH}$=), 3.3 (s,3,$CH_3O$), and
1.3-1.01 (m,15,$\underline{CH_3}CH_2O)_2P$ and -COOC$(CH_3)_3$).

5.9 Attempt to prepare tert-butyl 4-fluoro-2-methoxy-3-methyl-2-pentenoate (53)

A mixture of 3.76 g (0.0133 mole) of 52 and 0.56 g (0.0133 mole) of sodium hydride (57% dispersion in paraffin oil) in 20 ml of dioxane was heated at 80° for 10 hr. To the red solution, 1.2 g (0.0133 mole) of 3-fluoro-2-butanone was added, and the mixture was stirred for 2 hr, quenched with water, extracted with ether, and the extract was dried over magnesium sulfate for 15 min. The ether was removed under reduced pressure and the residue has the following proton nmr spectrum:

^{1}H nmr δ 6.0 (pair of quart.,$_{J=50Hz}$,1,CHF), 3.7 (s,3,CH_3O),
2.05 (s,3,CH_3C=), and
1.9-1.7 (m,12,$\underline{CH_3}$CHF and -COOC$(CH_3)_3$).

This spectrum is in a very good agreement with the structure of the expected product (53). But after 5 min of standing at room temperature, the very same sample decomposed with evolution of an acidic gas (presumably hydrogen fluoride), and the proton nmr spectrum of the decomposed product could not be interpreted.

5.10 Preparation of tert-butyl glyoxalate (55)[62]

A mixture of 12 g (0.0534 mole) of tert-butyl methoxybromoacetate and 5.5 g (0.0654 mole) of sodium bicarbonate in 65 ml of water

was stirred overnight at room temperature, extracted continuously with ether for two days, and the extract was dried over magnesium sulfate. Distillation afforded 3.5 g (44 per cent yield) of 55, bp 57-60° (20 mm). ^{1}H nmr δ 9.7 (s,1,-CHO) and 1.1 (s,9,-COOC$(CH_3)_3$).

5.11 Attempts to prepare Schiff's base from tert-butyl-glyoxylate and benzylamine

All attempts to prepare the compound mentioned above from equimolar amounts of 55 and benzyl amine failed due to the formation of very complex mixture which could not be identified.

5.12 Attempts to prepare tert-butyl diethylphosphono-N-benzylaminoacetate

Attempts to prepare mentioned compound from equimolar amounts of benzyl amine, diethyl phosphonate, and 55 failed.

5.13 Preparation of methyl nitroacetate

Fuming nitric acid was added dropwise to a mixture of 100 g (0.86 mole) of methyl acetoacetate in 54 g (0.4 mole) at 30°. The mixture was stirred at 30-35° for 1 hr and poured onto 1 kg of ice. The resulting solution was extracted with ether and the product was obtained in a 30 per centy yield, bp 104-109° (25 mm).

5.14 Preparation of methyl bromonitroacetate (56)

To a mixture of 30 g (0.252 mole) of methyl nitroacetate and

13.6 g (0.252 mole) of sodium methoxide in 60 ml of ether, 14 ml (0.25 mole) of bromine was added dropwise at 10°, and the mixture was kept at room temperature overnight. The precipitate was filtered, and after the ether has been evaporated, the product was obtained in 58 per cent yield, bp 113-118° (23 mm).

6.1 Attempt to prepare diethyl N,N-dibenzylaminomethylphosphonate (57a)

To an equimolar mixture of N,N-dibenzylamine and diethyl phosphonate, formaldehyde was added at a temperature below 85°. But the only product obtained was bis N,N-dibenzylamino methane:

^{1}H nmr δ 7.2 (s,20,Ph), 3.55 (s,8,-$\underline{CH_2}$Ph), and

3.0 (s,2,N-CH_2-N).

The very same compound was prepared from 2 moles of N,N-dibenzylamine and 1 mole of formaldehyde.

6.2 Preparation of diethyl N,N-diethylaminomethylphosphonate (57b)[68]

16.2 g (0.2 mole) of 37 per cent solution of formaldehyde was added to a mixture of equimolar amounts of diethylphosphonate and diethylamine at a temperature below 85°. The title compound was obtained in 65 per cent yield, bp 126-128° (20 mm).

^{1}H nmr δ 4.1 (quartet, 4,$CH_3\underline{CH_2}O)_2P$),

2.7 (m,6,=P$\underline{CH_2}N(\underline{CH_2}CH_3)_2$), 1.3 (t,6,-P($OCH_2\underline{CH_3}$)$_2$), and

1.0 (t,6,-N($CH_2\underline{CH_3}$)$_2$).

6.3 Attempt to exchange N,N-diethylamino- for N,N-dibenzylamino group in 57b[69]

A mixture of 57b and equimolar amounts of dibenzylamine and 0.1 M solution of hydrochloric acid was heated at reflux in ethanol for 1 hr but only the starting material was obtained.

7.1 Preparation of ethyl 4-fluoro-2-iodo-3-methylpentanoate (58)[72]

To 16 ml of a 0.62 M solution of lithium N,N-diisopropylamide in tetrahydrofuran (prepared from equimolar amounts of n-butyl lithium and diisopropylamine at -78°), 1.6 g (0.00987 mole) of ethyl 4-fluoro-3-methylpentanoate (20b) was added at 0° followed by the addition of 2 ml of hexamethylphosphoramide (HMPA). The mixture was then cooled to -78° and added by means of a syringe to a solution of 3.0 g (0.0118 mole) of iodine in 25 ml of tetrahydrofuran at -78°. After stirring for 5 min at the same temperature, the mixture was quenched with water, the organic layer was separated, and the aqueous layer was extracted three more times with ether. The extract was washed with water, with aqueous sodium bisulfite, and dried over magnesium sulfate. Distillation gave 58 in 15 per cent yield (0.42 g) bp 46-47° (0.005 mm).

^{1}H nmr δ 5.4-3.9 (m,4,CHF,CHI, and -COO$\underline{CH_2}CH_3$),

2.5-2.0 (m,1,$CH_3\underline{CH}$CHI), and

1.7-0.7 (m,9,$\underline{CH_3}$CHF,$\underline{CH_3}$CH, and -COO$\underline{CH_2}CH_3$).

^{19}F nmr multiplet at -6.27 and -8.96, heptet at -21.79 and -26.27.

7.2 Preparation of ethyl 2-bromo-4-fluoro-3-methylpentanoate (59)

In the same manner as described above, the title compound was prepared in 16.6 per cent yield (1 g) bp 41-45° (0.02 mm):

^{1}H nmr δ 5.5-4.1 (m,4,CHBr,CHF, and -COO$\underline{CH_2}CH_3$),

2.6-1.9 (m,1,$CH_3\underline{CH}$CHBr) and 1.6-0.8 (m,9,CH_3CHF,$\underline{CH_3}$CH and -COO$CH_2\underline{CH_3}$).

^{19}F nmr multiplets at -9.55 and -11.94, and
heptets at -22.39 and -29.25

7.3 Preparation of methyl 2-bromo-4-fluoro-3-methylpentanoate (60)

This compound was prepared in the same manner as above, in 16 per centy yield, bp 29-31° (0.005 mm)

^{1}H nmr δ 5.5-4.0 (m,2,CHF and CHBr), 3.75 (s,3,-$COOCH_3$),
2.6-1.8 (m,1,$CH_3\underline{CH}CHBr$), and
1.6-0.8 (m,6,$\underline{CH_3}CHF$ and $\underline{CH_3}CH$);

^{19}F nmr multiplets at -9.85 and 11.94, and
heptets at -22.98 and 29.85.

7.4 Preparation of tert-butyl 2-bromo-4-fluoro-3-methylpentanoate (61)

In the manner described above, the title compound was prepared in 16.6 per cent yield, bp 58-59° (0.15 mm):

^{1}H nmr δ 5.2-4.1 (m,2,CHF and CHBr), 2.5-2.2 (m,1,$CH_3\underline{CH}CHF$),
1.5 (s,9,-$COOC(CH_3)_3$) and
1.4-0.8 (m,6,$\underline{CH_3}CHF$ and $\underline{CH_3}CH$).

^{19}F nmr two multiplets at -9.55 and -12.84
and two heptets at -23.28 and -29.85.

7.5 Preparation of ethyl 2-azido-4-fluoro-3-methylpentanoate 62)

1.6 g (0.0066 mole) of 59 and 0.52 (0.008 mole) of sodium azide was heated at reflux in 30 ml of methanol overnight to give 1.22 g (91 per cent yield) of 62, bp 40-42° (0.025 mm).

^{1}H nmr δ 5.1-3.3 (m,4,CHF,CHN_3, and -$COOCH_2CH_3$),
2.5-1.6 (m,1,CHF$CH$$CHN_3$), and
1.6-0.6 (n,9,CH_3CHF,CH_3CH, and -$COOCH_2CH_3$).

^{19}F nmr multiplets at -9.25 and -11.64,
heptets at -22.39 and -29.25.

IR very strong band at 2125 cm^{-1} (n_3).

7.6 Preparation of tert-butyl 2-azido-4-fluoro-3-methylpentanoate (23c)

The title compound was prepared in 95 per cent yield (not distilled) as described above.

IR very strong band at 2125 cm^{-1} (N_3).

7.7 Preparation of ethyl 2-amino-4-fluoro-3-methylpentanoate (5)

Catalytic hydrogenation of 23c in 25 ml of ethanol over 0.2 g of palladium on carbon under the hydrogen pressure of 4 atm gave 60 per cent of 5, bp 38-41° (0.025 mm).

^{1}H nmr δ 5.0-3.3 (m,4,CHF,$CHNH_2$, and -$COOCH_2CH_3$),
2.8-1.9 (m,3,CHFCH-$CHNH_2$) and
1.6-0.7 (m,9,CH_3CHF,CH_3CH, and -$COOCH_2CH_3$).

^{19}F nmr multiplets at -10.75 and -13.73,

heptets at -20.60 and -24.92.

IR broad peak at 3400 cm^{-1} and disappearance of peak at 2125 cm^{-1}.

7.8 Preparation of tert-butyl 2-amino-4-fluoro-3-methylpentanoate (24c)

The title compound was prepared in 60 per cent yield as described above, using 30 atm pressure of hydrogen for 24 hr. The product had bp 48-50° (0.025 mm):

^{19}F nmr multiplets at -10.45 and -13.13

heptets at -19.40 and -23.28.

IR broad band at 3400 cm^{-1} and disappearance of band at 2125 cm^{-1}.

7.9 Preparation of 2-amino-4-fluoro-3-methylpentanoic acid (1)

0.5 g of 24c was dissolved in 25 ml of trifluoroacetic acid and stirred overnight at room temperature. The crystalline product was woluble in water, showed four sets of peaks in ^{19}F nmr, and gave positive ninhydrin test.

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APPENDIX

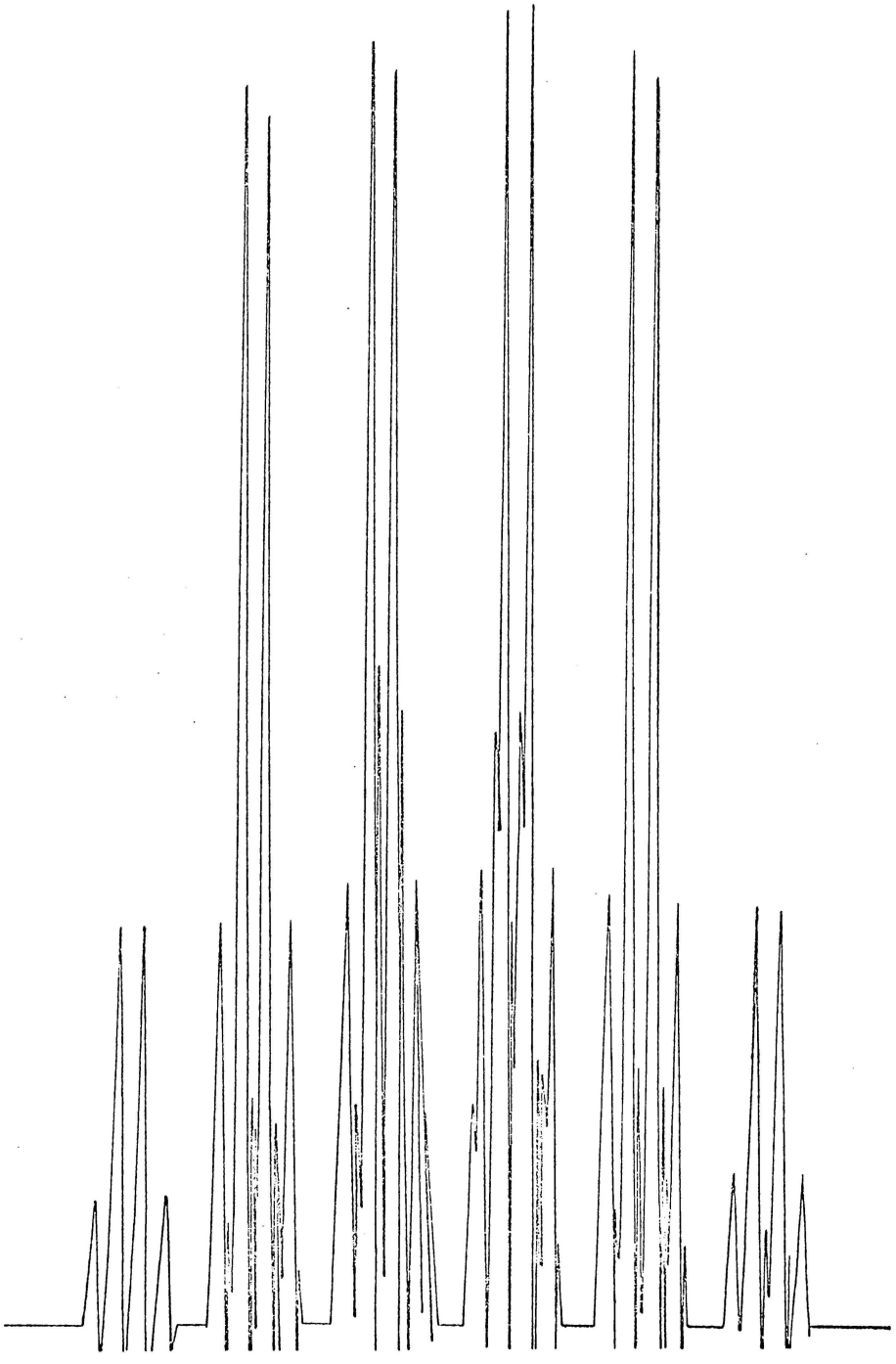


Fig. 1 ^{19}F nmr spectrum of 3-fluoro-2-butanone (expanded to 540 Hz)

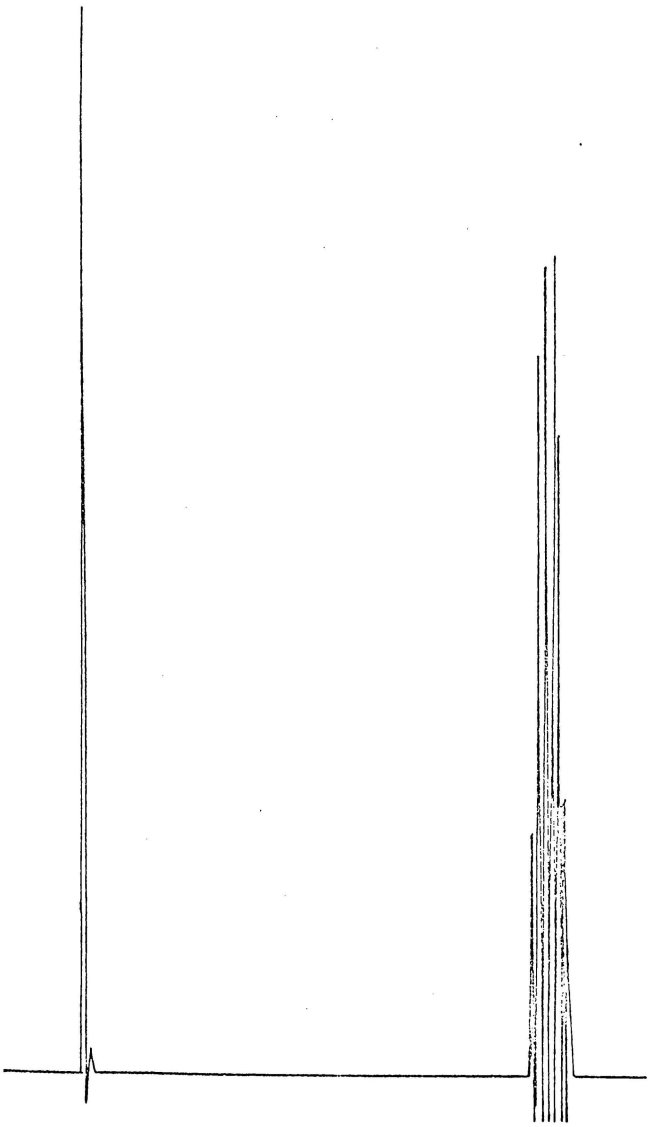


Fig. 2 ^{19}F nmr spectrum of 3-fluoro-2-butanone

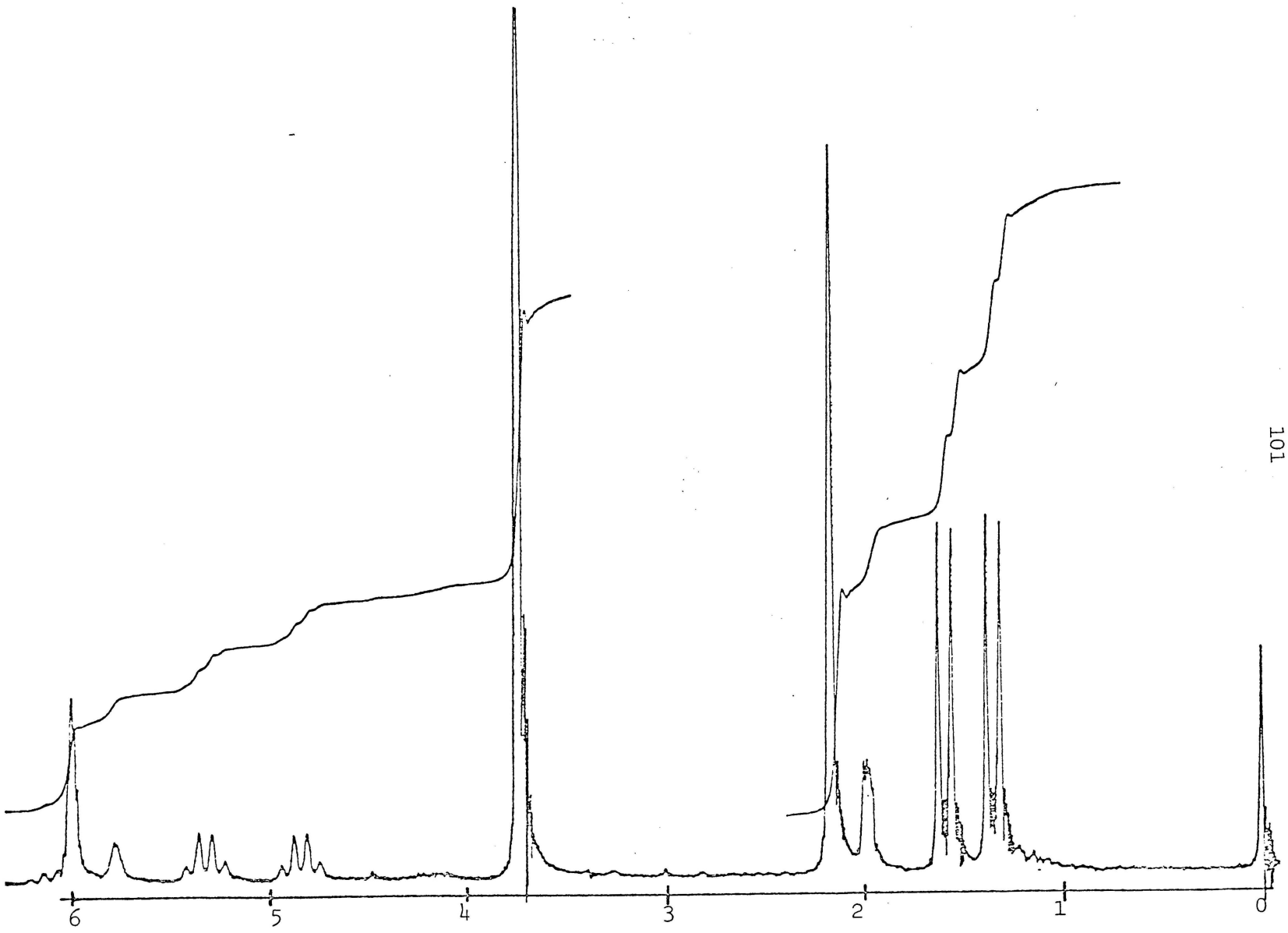


Fig. 3 ^{1}H nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate

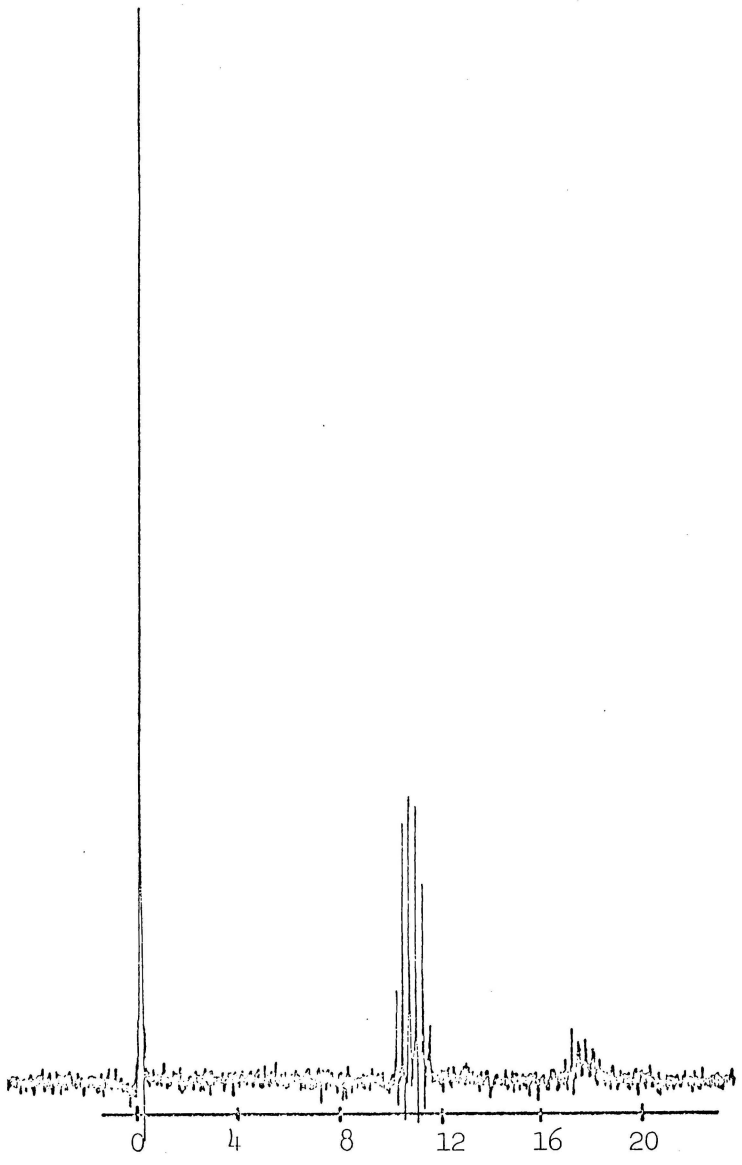


Fig. 4 ^{19}F nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate

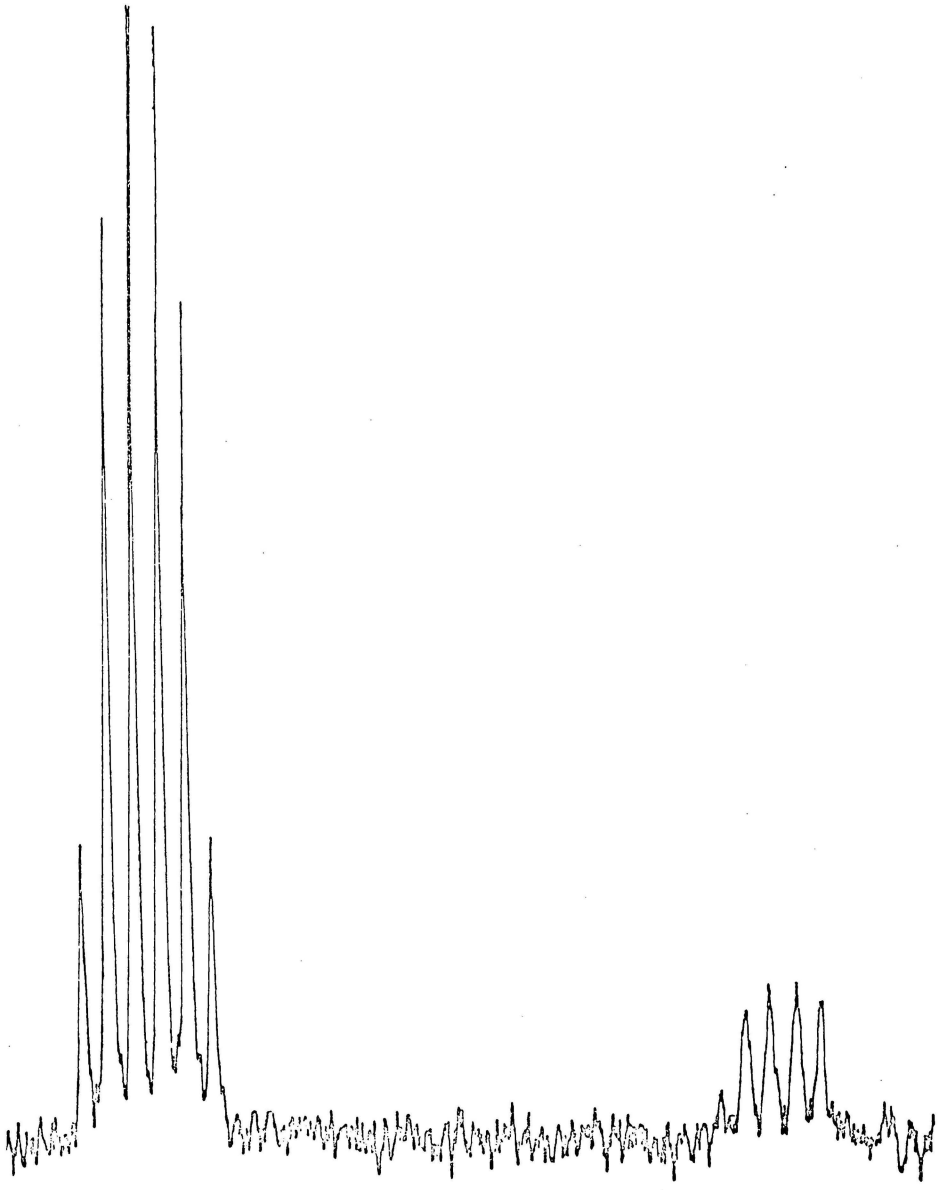


Fig. 5 ^{19}F nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate (expanded to 2700 Hz)

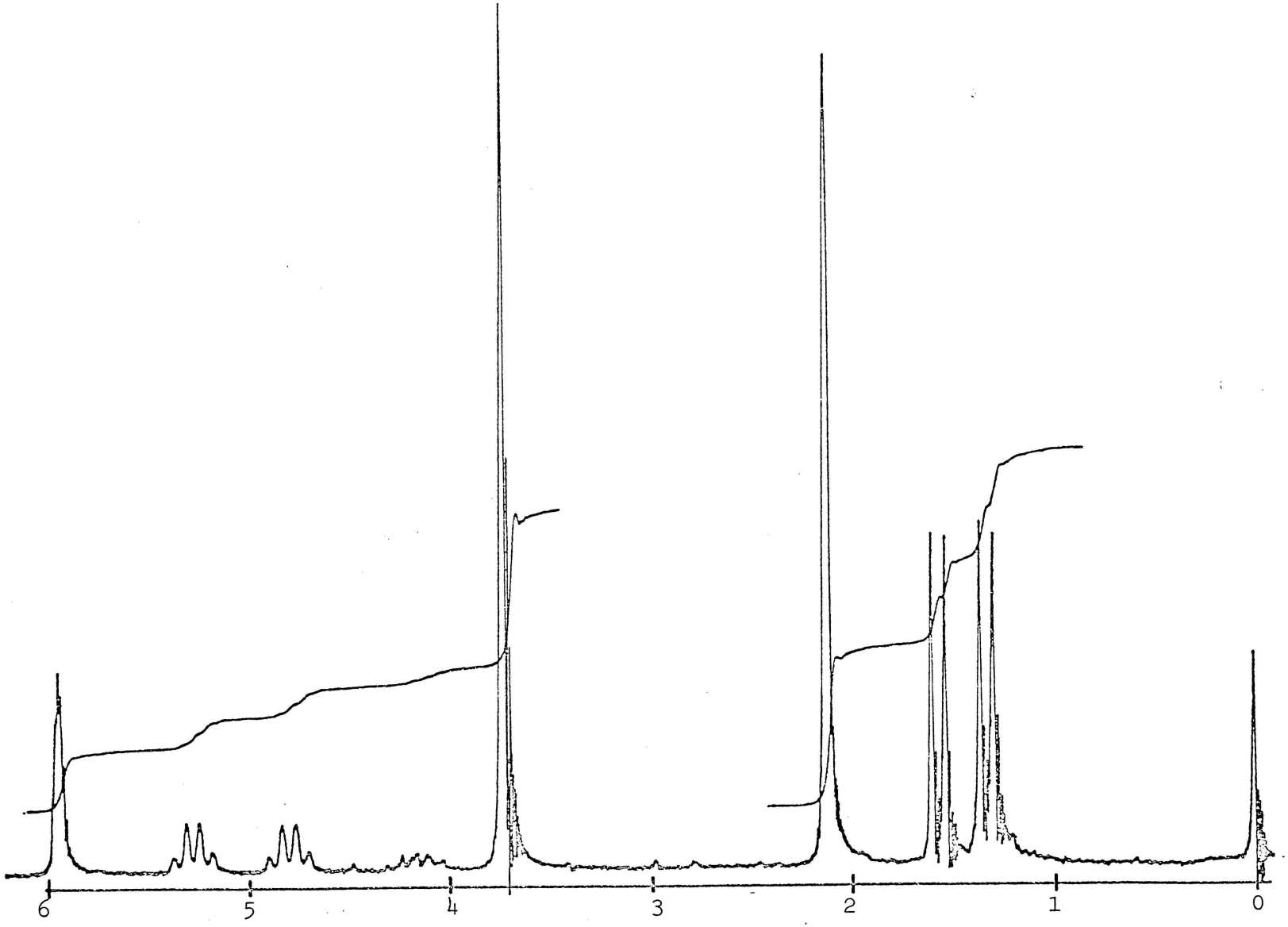


Fig. 6 ^{1}H nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate (pure E form)

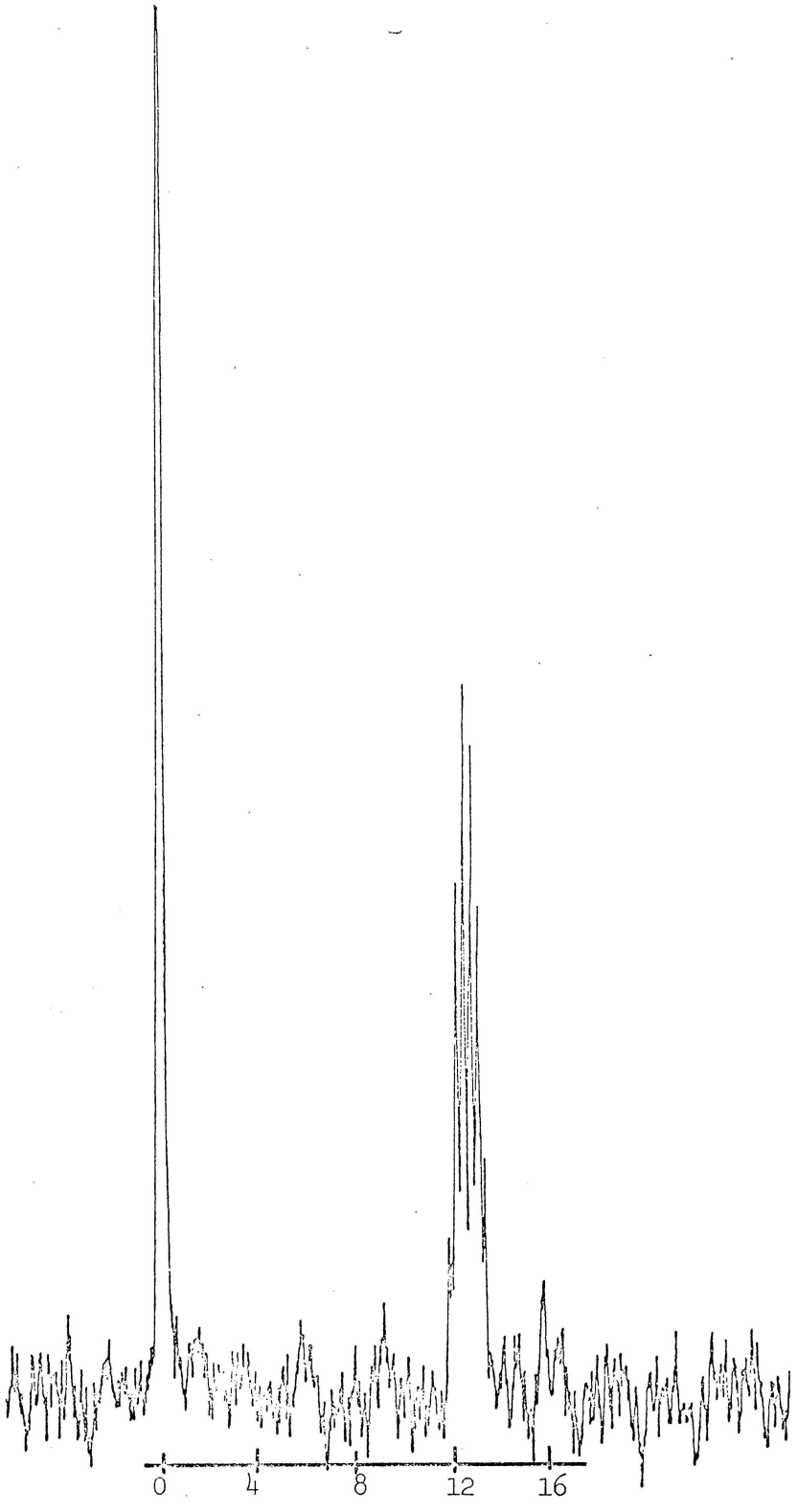


Fig. 7 ^{19}F nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate (pure E form)

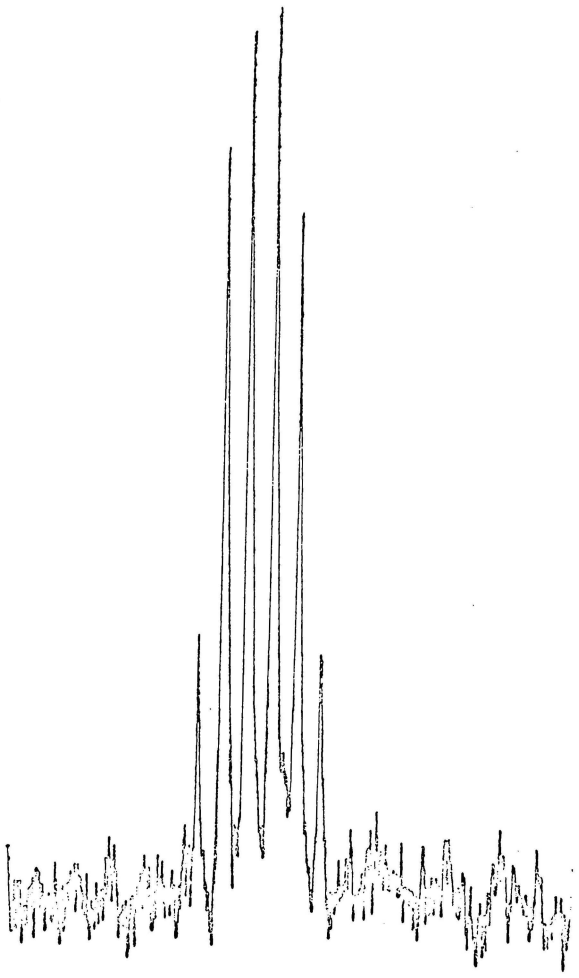


Fig. 8 ^{19}F nmr spectrum of Methyl 4-fluoro-3-methyl-2-pentenoate (pure E form-expanded to 2700 Hz)

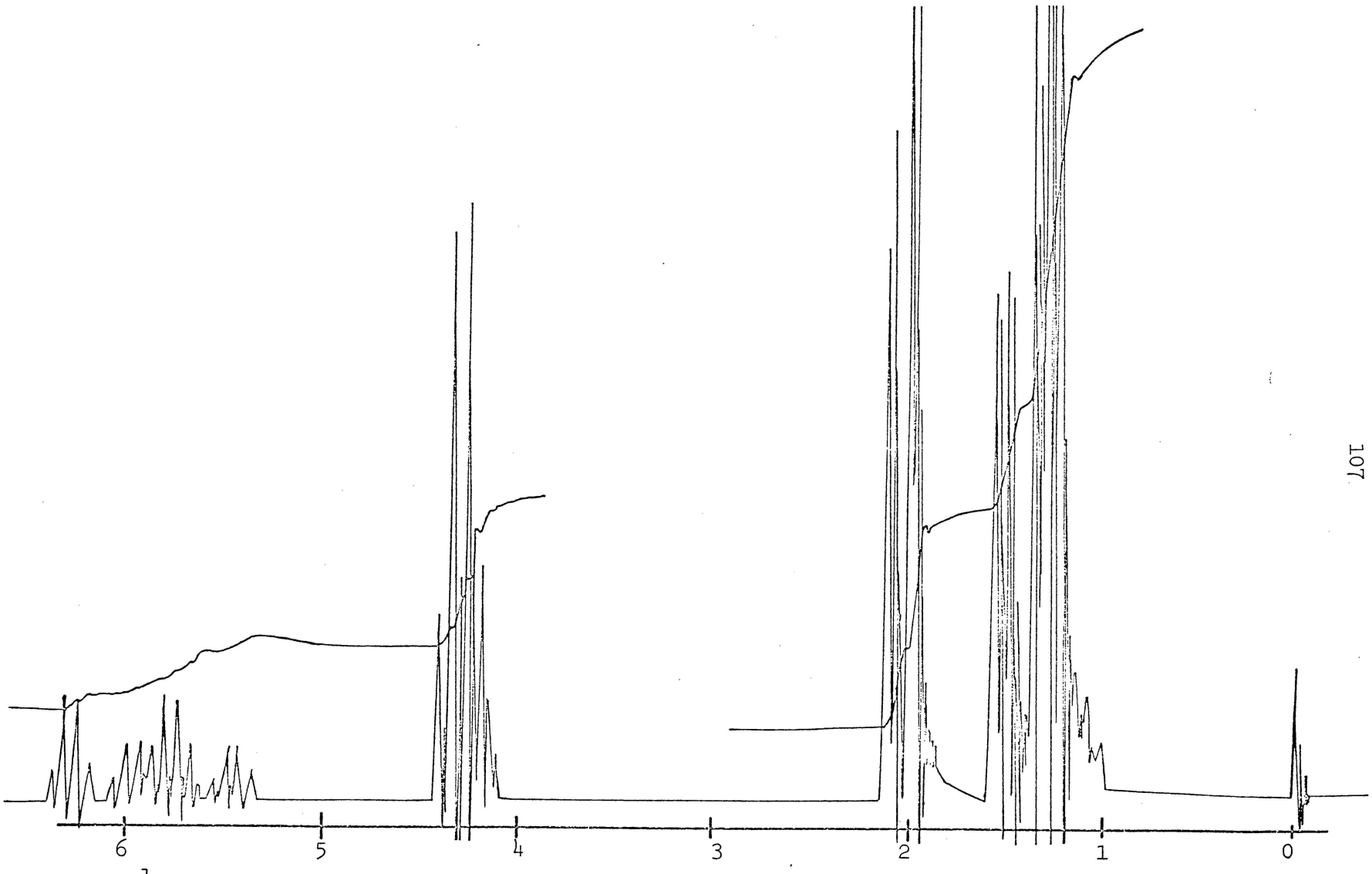


Fig. 9 ^{1}H nmr spectrum of Ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate

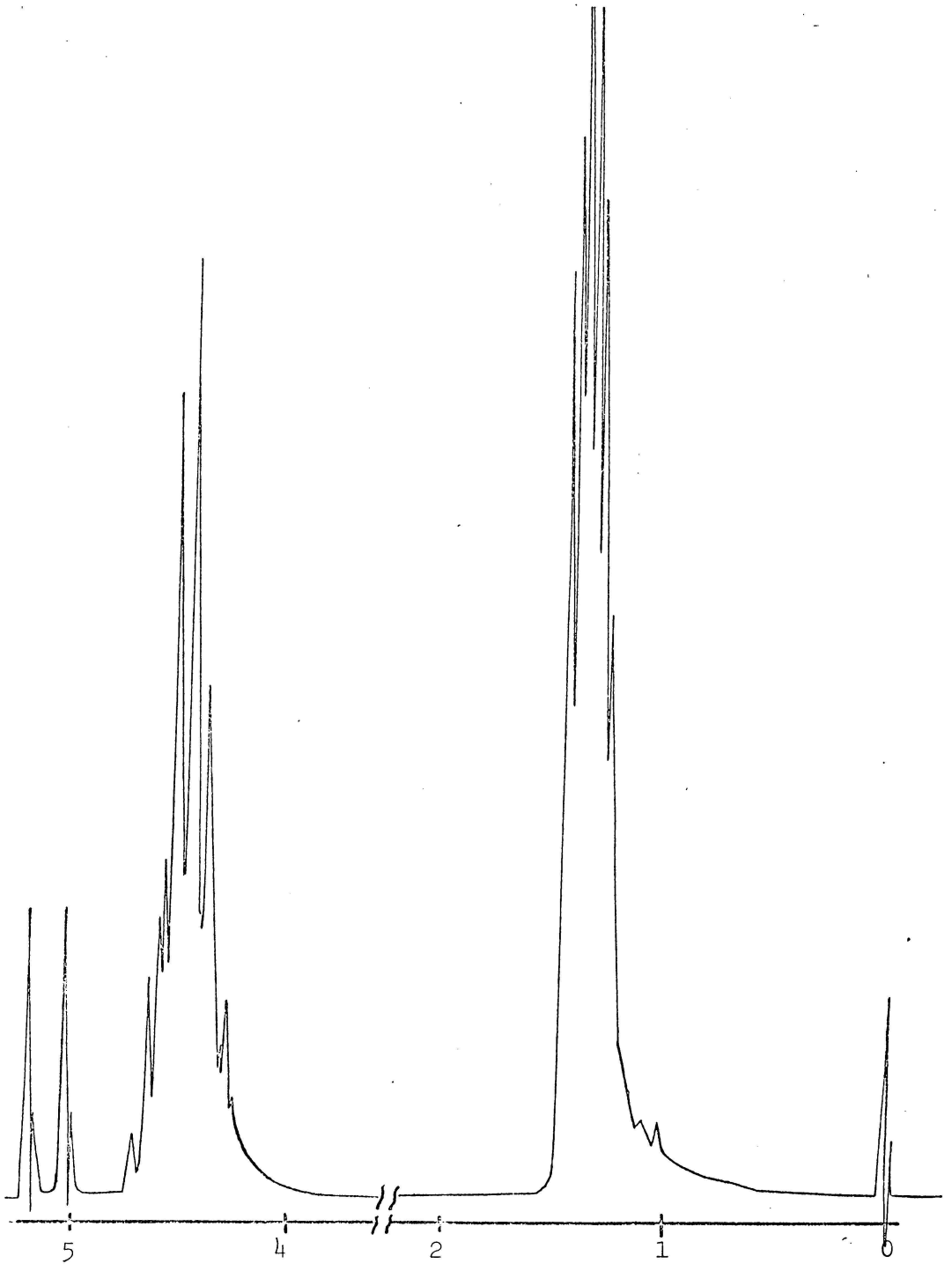


Fig. 10 ^{1}H nmr of Ethyl diethylphosphonochloroacetate

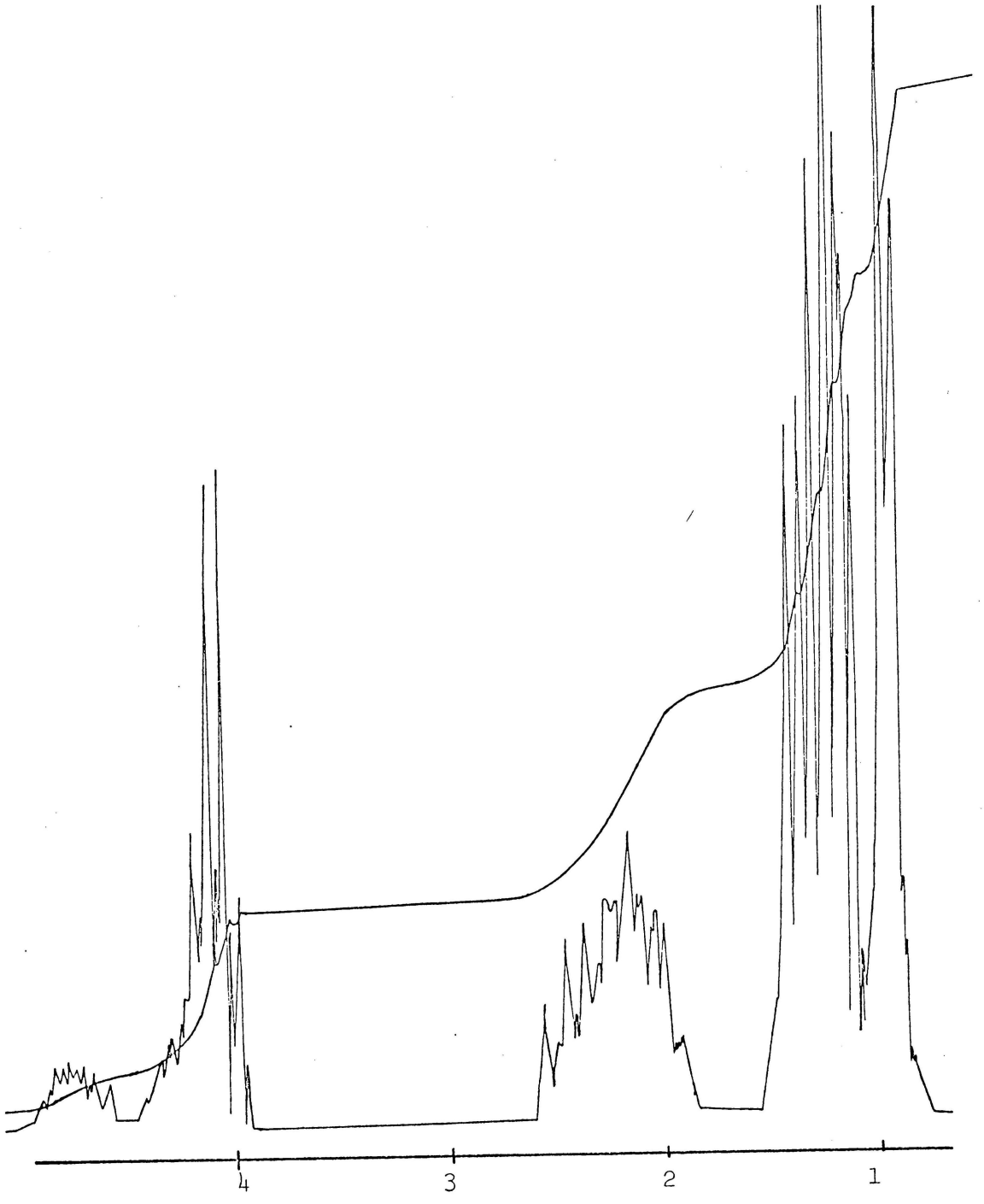


Fig. 11 ^{1}H nmr spectrum of Ethyl 4-fluoro-3-methylpentanoate

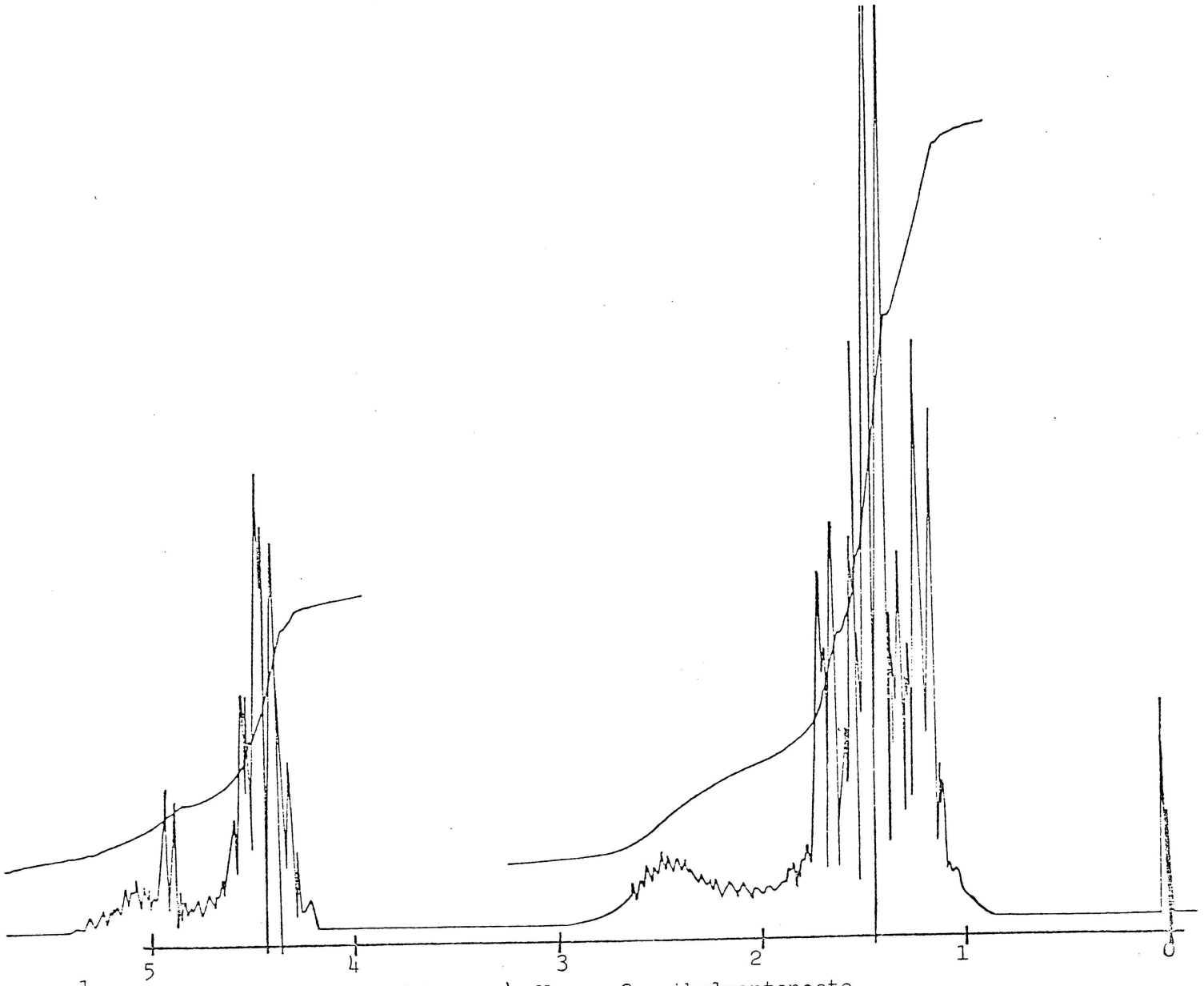


Fig. 12 ^{1}H nmr spectrum of Ethyl 2-bromo-4-fluoro-3-methylpentanoate

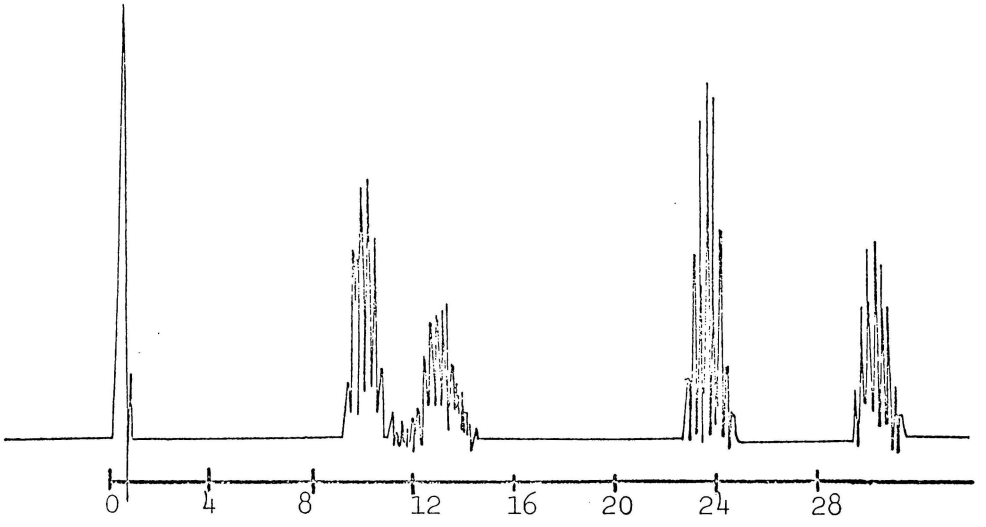


Fig. 13 ^{19}F nmr spectrum of Ethyl 2-bromo-4-fluoro-3-methylpentanoate

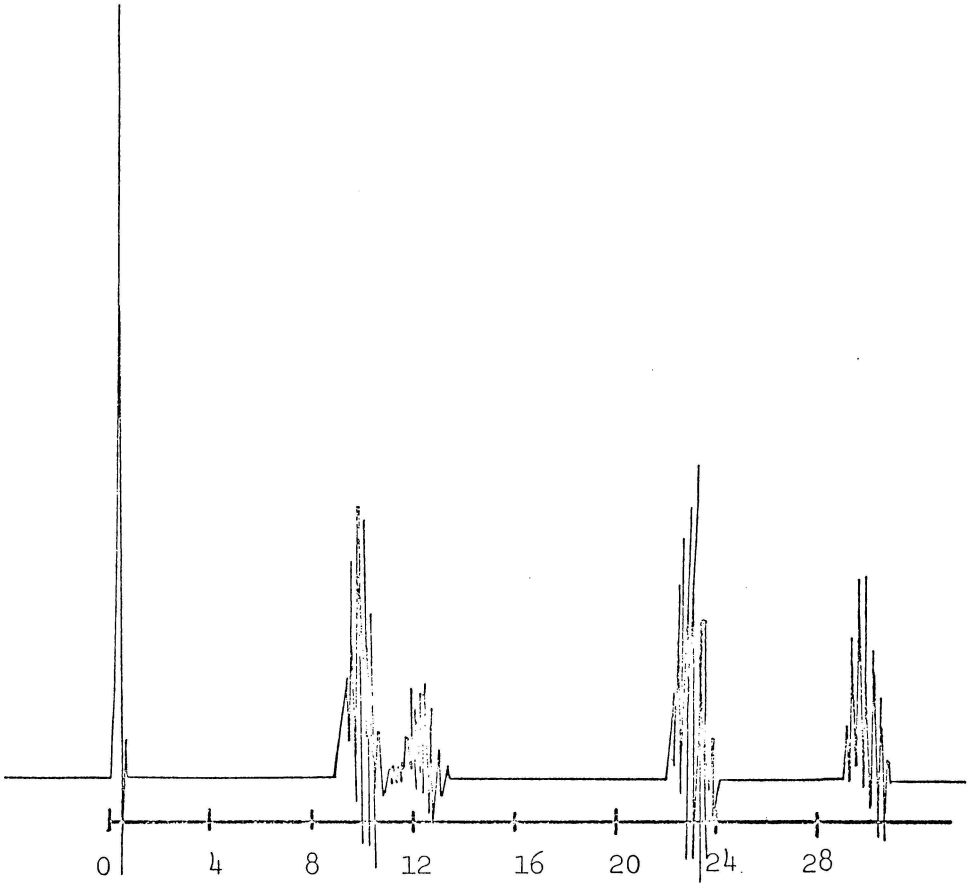


Fig. 14 ^{19}F nmr spectrum of tert-Butyl 2-bromo-4-fluoro-3-methylpentanoate

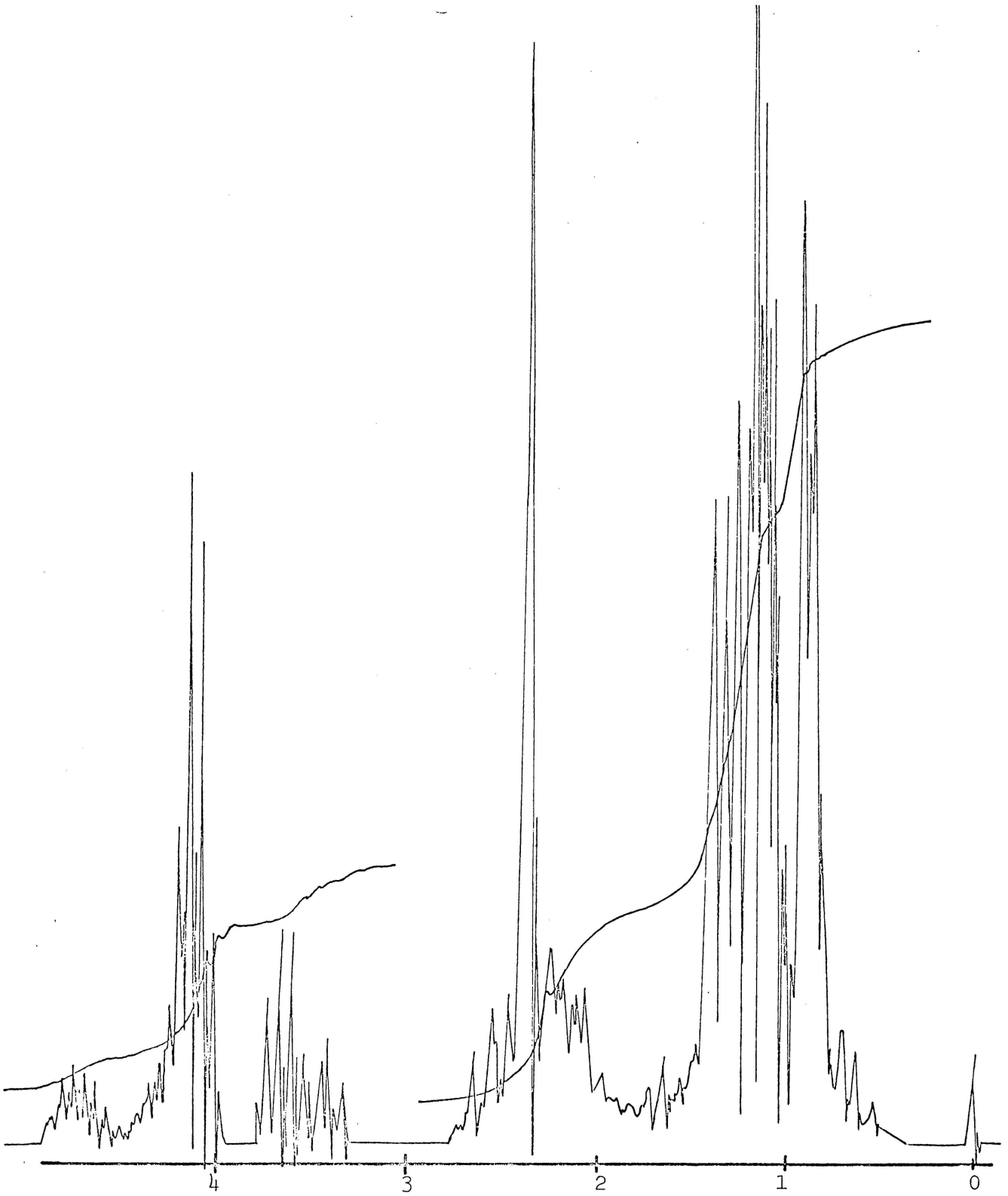


Fig. 15 ^{1}H nmr spectrum of Ethyl 2-amino-4-fluoro-3-methylpentanoate

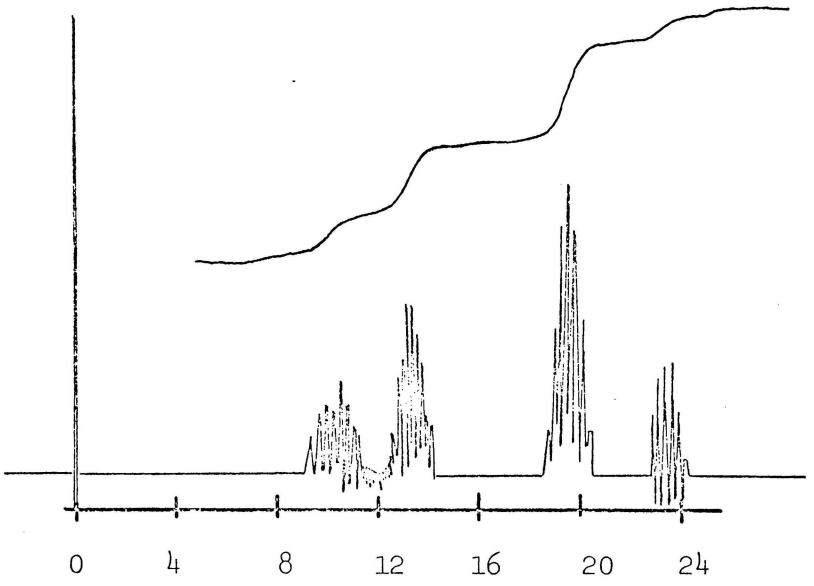


Fig. 16 ^{19}F nmr spectrum of tert-Butyl 2-amino-4-fluoro-3-methylpentanoate

TABLE I

ATTEMPTS TO ALKYLATE ACETOACETATE AND MALONATES WITH 2-BROMO-3-FLUOROBUTANE

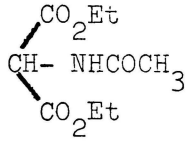
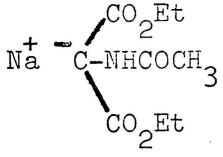
Active methylene compound	SOLVENT	BASE	CATALYST	TEMP.	TIME	RESULT
$CH_3COCH_2CO_2Et$	Diglyme	NaOEt	NaI	100°	4 hr	N.R.
	Monoglyme	NaH	NaI	110°	4 hr	loss of fluorine
	Sulfone	NaH	NaI	110°	24 hr	loss of fluorine
	DMf	NaH		120°	4 hr	loss of fluorine
	Monoglyme	NaH	NaI	Reflux	4-24 hr	N.R.
	2-Bromo-3-fluorobutane			Sealed tube 80-120°	3-8 hr	loss of fluorine

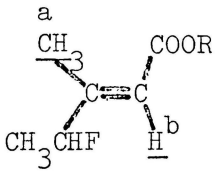
TABLE II

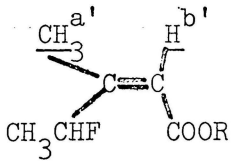
ATTEMPTS TO CENVERTE 3-HYDROXY-2-BUTANONE TO 3-FLUORO-2-BUTANONE

Reagent	Solvent	Temp.	Ref.
Et_2NCF_2CHFCl	ether	R.T.	(13)
$PhPF_4$	none	120^o	(24)
$SOCl_2$	benzene	reflux	(25)
p-TxCl	benzene	reflux	(26)
PBr_3	benzene	-10^o	(27)

TABLE III

The position and the ratio of methyl- and vinylic protons of alkyl 4-fluoro-3-methyl-2-pentenoates in ^{1}H nmr spectrum





R	a	a'	b	b'	a/a'	b/b'
Me	2.03	1.85	5.75	5.58	77/23	75/25
Et	2.5	2.4	6.15	5.95	78/22	74/26
ter-Bu	2.05	1.95	5.75	5.6	76/24	75/25
$PhCH_2$	2.05	1.95	5.95	5.7	75/27	76/24

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FLUORINATED AMINO ACID DERIVATIVES

by

Darko Butina

(ABSTRACT)

A new approach in the syntheses of 3-bromo-2-butanone and 2-bromo-3-fluorobutane has been developed. All attempts to alkylate the sodium salt of diethyl malonate, ethyl acetoacetate, or diethyl acetamidomalonate with 2-bromo-3-fluorobutane failed.

New phosphonoacetates, tert-butyl and benzyl diethylphosphonoacetates were prepared as very versatile intermediates in the syntheses of carboxylic acids.

Methyl-, ethyl-, tert-butyl-, and benzyl 4-fluoro-3-methyl-2-pentenoates were synthesized in high yields by the Horner-Emmons reaction.

The reaction is stereoselective and gave E and Z form in 75:25 ratio as determined from proton and fluorine nmr spectra.

A long range coupling was observed in fluorine nmr spectrum of 3-fluoro-2-butanone.

From the ethyl 4-fluoro-3-methyl-2-pentenoate, ethyl 2-bromo-4-fluoro-3-methyl-2-pentenoate was prepared, but the latter could not be reduced under the conditions of catalytic hydrogenation.

Ethyl 2-chloro-4-fluoro-3-methyl-2-pentenoate was prepared from 3-fluoro-2-butanone and ethyl diethylphosphonochloroacetate, but could

not be reduced.

Catalytic hydrogenation of alky 4-fluoro-3-methyl-2-pentenoates gave the corresponding saturated esters in high yields.

Treatment of alkyl 4-fluoro-3-methylpentanoates with lithium diisopropylamide and bromine at -78° yielded the corresponding 2-bromoderivatives.

Methyl-, ethyl-, and tert-butyl 2-bromo-4-fluoro-3-methyl-pentanoates were treated with sodium azide to give the corresponding 2-azido derivatives which were further reduced into methyl-, ethyl-, and tert-butyl 2-amino-4-fluoro-3-methylpentanoates.