Enol and Acyl Phosphates as Intermediates in the Synthesis of Nonrandom Triglycerides

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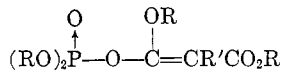
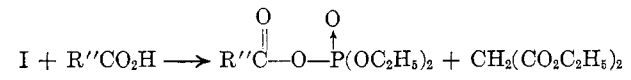
Trialkyl phosphites and dialkyl bromomalonates have been reported to react at 0° to give enol phosphates or at 150° to give phosphonomalonates. However, examination of infrared and n.m.r. spectra of trialkyl phosphite–dialkyl bromomalonate reaction products has failed to provide any evidence of phosphonomalonate formation. Instead, enol phosphates are produced at both temperatures. Fatty acyl phosphates, which can be prepared from the enol phosphate, 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I), and fatty acids, were investigated as potential esterification reagents for making glycerides of known structure. It was found that diethyl oleoyl phosphate reacts with 1,3-dipalmitin in the presence of perchloric acid to give a 92% yield of triglyceride. It was further found that approximately 90% of the oleic acid was esterified at the 2-position of the triglyceride.

There are several reports in the literature concerning the chemistry of enol phosphates.[1] One particularly reactive compound of this type, 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I), has been studied



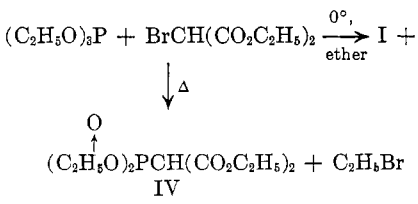
I, R = C_2H_5; R′ = H
II, R = CH_3; R′ = H
III, R = C_2H_5; R′ = CH_3

in some detail by Cramer and co-workers,[2] who have found that this enol phosphate reacts smoothly with



carboxylic acids to give acyl phosphates. The reported[2a] effectiveness of these acyl phosphates as acylating agents for amines and amino acids prompted this investigation of their use as intermediates in the synthesis of nonrandom triglycerides.

Synthesis and N.m.r. Spectra of Enol Phosphate Intermediates.—The reaction of diethyl bromomalonate with triethyl phosphite has been presumed to give one of two products depending on the reaction conditions. The Perkow reaction, leading to I, occurs at 0° in ether[2a] while a Michaelis–Arbuzov reaction, resulting in the formation of tetraethyl phosphonomalonate (IV), reportedly takes place at elevated temperatures in the absence of solvent.[3] It has now been found,

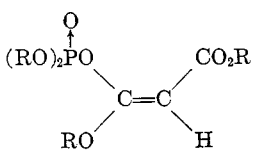


however, that the reaction takes only one course and that the product formed at either temperature is the enol phosphate.

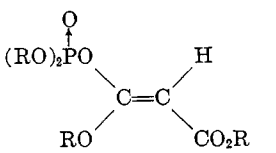
The infrared spectrum of I is characterized by absorption at 1647 (C=C conjugated with C=O) and 1718 cm.$^{-1}$ (ester C=O).[2a] The proton and phosphorus n.m.r. spectra have not been reported previously. The P^{31} resonance occurs in the phosphate region of the spectrum at +8.9 p.p.m.[4] The H^1 spectrum is reproduced in Figure 1. While it was possible to assign the doublets (H^1–P^{31} spin coupling) at τ 5.49 (J = 1.1 c.p.s.) and 5.15 (J = 1.8 c.p.s.) in Figure 1 to the vinyl proton resonances of I, the relatively high upfield shift of these bands, their proximity to the $-OCH_2-$ bands, and the initial uncertainty as to the product(s) formed from the reactions of trialkyl phosphites and dialkyl bromomalonates made it desirable to synthesize the analogous enol phosphates, 2-carbomethoxy-1-methoxyvinyl dimethyl phosphate (II) and 2-carbethoxy-1-ethoxy-1-propenyl diethyl phosphate (III), whose spectra are more easily interpreted.

The phosphorus spectrum of II shows the expected septet, centered at +6.6 p.p.m., with a spin coupling constant between the protons and the phosphorus in the $(CH_3O)_2P\rightarrow O$ group of 10.8 c.p.s. In the proton spectrum of II (Figure 2), the four bands which appear at τ 6.0–6.5 are due to CH_3O- protons. Two of these bands, τ 6.21 and 6.39 (J = 10.8 c.p.s.), comprise the $(CH_3O)_2P\rightarrow O$ doublet. Further assignment of the other two, one arising from the $CH_3OC{=}C-$ group and the other from the $-CO_2CH_3$ group, was not made. The vinyl proton resonance of II appears as a doublet at τ 5.35 (J = 1.0 c.p.s.) and another doublet at τ 5.16 (J = 1.8 c.p.s.). The total area under these peaks is proportional to one proton. The enol phosphate III has no vinyl proton and, correspondingly, its proton spectrum (Figure 3) shows no bands below τ 5.50.

The occurrence of two olefinic proton bands in the spectra of I and II is attributable to the presence of the two geometrical isomers V and VI. Previous



Va, R = C_2H_5
b, R = CH_3



VIa, R = C_2H_5
b, R = CH_3

(1) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).

(2) (a) F. Cramer and K. G. Gärtner, *Chem. Ber.*, **91**, 704 (1958); (b) F. W. Lichtenthaler and F. Cramer, *ibid.*, **95**, 1971 (1962).

(3) (a) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **68**, 1103 (1946); (b) A. E. Arbuzov and G. Kamai, *Zh. Obshch. Khim.*, **17**, 2149 (1947); *Chem. Abstr.*, **42**, 4523 (1948); (c) A. N. Pudovik and T. M. Moshkina, *Zh. Obshch. Khim.*, **27**, 1611 (1957); *Chem. Abstr.*, **52**, 3712 (1958).

(4) The P^{31} n.m.r. spectra in this report were measured at 24.3 Mc./sec. on a modified Varian Model HR-60 spectrometer. The chemical shifts are expressed in parts per million with an external reference from 85% orthophosphoric acid. The proton n.m.r. spectra were obtained on a Varian A-60 spectrometer at 60 Mc./sec. Their chemical shifts (τ) are relative to the internal standard, tetramethylsilane (τ 10.00).

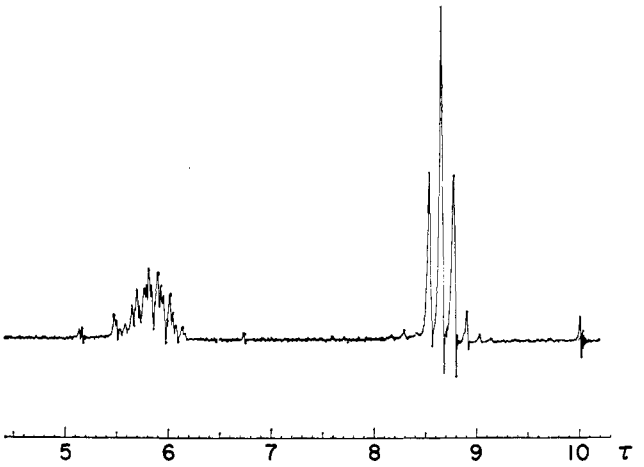


Figure 1.—N.m.r. spectrum of 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I).

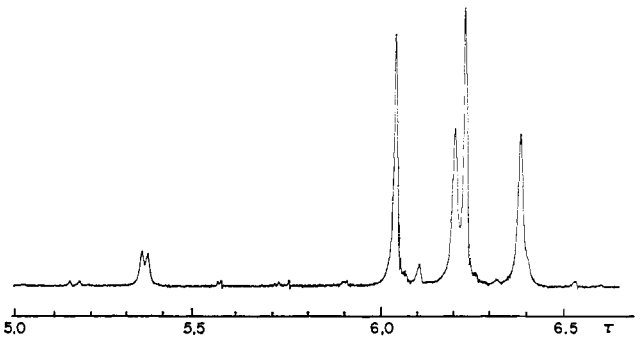
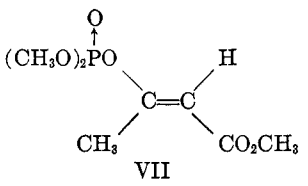
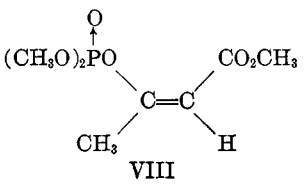


Figure 2.—N.m.r. spectrum of 2-carbomethoxy-1-methoxyvinyl dimethyl phosphate (II).

workers[5,6] have shown that the chemical shift of the =CH resonance in α-Phosdrin® (VII) is τ 4.24[7] ($J_{H^1\text{-}P^{31}}$ = 1.8 c.p.s.) while that of the =CH resonance in β-Phosdrin® (VIII) is τ 4.53 (J = 0.9 c.p.s.). In

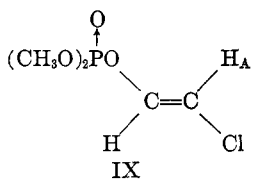


VII

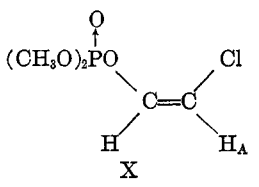


VIII

addition, Stiles, *et al.*,[5] have measured the proton n.m.r. spectrum of a mixture of *cis*- and *trans*-2-chlorovinyl dimethyl phosphate and have assigned the resonance at τ 3.63 to the H_A of the *trans* isomer IX and the resonance at τ 4.16 to the H_A of the *cis* isomer X.



IX



X

Unequal amounts of the geometrical isomers V and VI were formed in all of the present enol phosphate

(5) A. R. Stiles, C. A. Reilly, G. R. Pollard, C. H. Tieman, L. F. Ward, Jr., D. D. Phillips, S. B. Soloway, and R. R. Whetstone, *J. Org. Chem.*, **26**, 3960 (1961).

(6) T. R. Fukuto, E. O. Hornig, R. L. Metcalf, and M. Y. Winton, *ibid.*, **26**, 4620 (1961).

(7) τ values for the chemical shifts in α- and β-Phosdrin® and in *cis*- and *trans*-2-chlorovinyl dimethyl phosphate have been calculated from the cycles per second and parts per million values which appeared in the original papers.

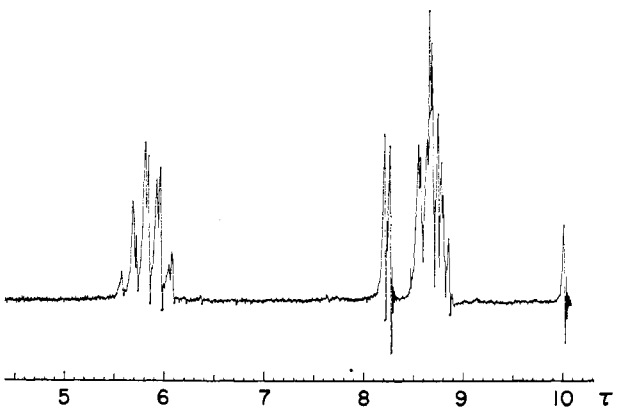
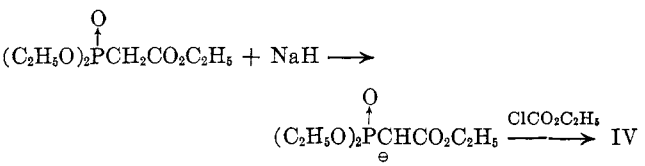


Figure 3.—N.m.r. spectrum of 2-carbethoxy-1-ethoxy-1-propenyl diethyl phosphate (III).

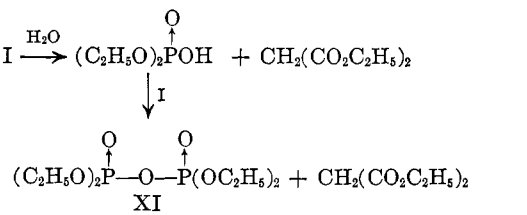
syntheses. The more abundant isomer in each case was the one in which the olefinic proton resonance occurs at higher applied field and in which there is a smaller H^1–P^{31} spin coupling constant. On the basis of the above relationships, structure V can be assigned to this predominant isomer.

One of the procedures described for the synthesis of tetraethyl phosphonomalonate,[3a] heating triethyl phosphite and diethyl bromomalonate at 150° for 4 hr., was repeated. In contrast to the previous conclusions,[3] however, infrared and n.m.r. spectra of the product obtained from this reaction were identical in every respect with those of I. As a further check on the course of reactions between trialkyl phosphites and dialkyl bromomalonates, an alternative synthesis of tetraethyl phosphonomalonate (IV) from triethyl phosphonoacetate, sodium hydride, and ethyl chloroformate was carried out. The P^{31} resonance in the au-



thentic phosphonate is shifted to −12.8 p.p.m. No proton resonance occurs below τ 5.59 nor is there any infrared absorption in the olefinic double bond region. Since no evidence of P^{31} resonance at −12.8 p.p.m. could be found in the spectra of any of the triethyl phosphite–diethyl bromomalonate reaction mixtures, it is concluded that the reported syntheses of tetraethyl phosphonomalonate from these reactants are erroneous.

During the course of the present work it was noticed that the P^{31} spectra of several samples of I contained a band at +12.6 p.p.m. in addition to the one at +8.9 p.p.m. The presence of this band indicates contamination of the sample by tetraethyl pyrophosphate (XI). Formation of this impurity is initiated by exposure to moisture and has been shown to take place very

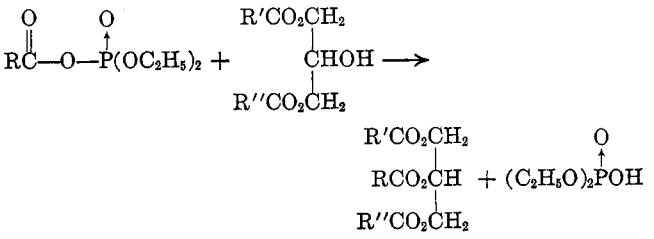


XI

rapidly.[2] It is still worth emphasizing, however, that the enol phosphate, once contaminated, is extremely difficult to purify. Attempts at fractional distillation of impure products usually resulted in decomposition of most of the enol phosphate.

Synthesis of Nonrandom Triglycerides from Acyl Phosphates.—Since most of the standard esterification processes must be carried out under conditions which promote rearrangement of diglycerides to equilibrium mixtures of the 1,3 and 1,2 isomers, few methods exist for the preparation of nonrandom triglycerides. The only method which finds widespread use at the present time employs acid chlorides in the presence of pyridine. However, fatty acid chlorides react relatively slowly and complete removal of the pyridine, which must be used in order to suppress isomerization, is often difficult. A much improved synthesis has recently been developed by Mattson, *et al.*[8] They have found that perchloric acid catalyzed acylations of diglycerides with fatty acid anhydrides lead to excellent yields of single triglycerides, although perchloric acid by itself will cause diglyceride isomerization. The success of this process was attributed to a rate of acylation which far exceeds the rate of isomerization. It was, in fact, found that esterification was essentially complete in 5 min. While this method offers a rapid route to specific triglycerides, it also has some disadvantages. For each mole of anhydride that reacts, a mole of residual fatty acid is produced. Thus, the process is not only inefficient in its use of fatty acid but also, and more importantly, in many cases yields a mixture from which a pure product can be isolated only by repeated recrystallization.

The use of acyl phosphate intermediates could eliminate the above difficulties. If good yields of nonisomerized triglycerides were obtainable from acyl phosphate acylations, the method would offer greater utilization of the fatty acid component and would give a by-product, diethyl hydrogen phosphate, which could be removed by water washing and/or a single recrystallization of the triglyceride.



Four reactions of 1,3-dipalmitin and diethyl oleoyl phosphate are compared in Table I. The acyl phosphate used in the first three reactions was prepared from oleic acid of at least 99% purity and 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I) which had been freshly prepared but which had not been distilled. Reaction IV differed in that the enol phosphate was distilled before synthesis of the acyl phosphate. In each case, the resulting acyl phosphate was used without isolation or purification for the esterification reaction. The fatty acid composition at the 2-position of each triglyceride was determined by lipase hydrolysis.[9]

(8) F. H. Mattson, R. A. Volpenhein and J. B. Martin, *J. Lipid Res.*, **5**, 374 (1964).

(9) F. H. Mattson and R. A. Volpenhein, *ibid.*, **2**, 58 (1961).

TABLE I

REACTIONS OF 1,3-DIPALMITIN WITH DIETHYL OLEOYL PHOSPHATE

Reaction	Catalyst	Temp., °C.	Time, hr.	Triglyceride Yield, % (based on diglyceride)	Triglyceride 2-Position oleic acid, %
I	None	26	Overnight	51	57
II	$HClO_4$	26	3.5	79	91
III	$HClO_4$	50	3.5	78	90
IV	$HClO_4$	26	4	92	87

Acyl phosphates are essentially mixed anhydrides of a carboxylic and a phosphoric acid and it is quite apparent from the results contained in Table I that perchloric acid also exerts a catalytic effect on their reactivity. First of all, the data from reaction IV show that triglyceride yields of greater than 90% are obtainable from catalyzed reactions when distilled enol phosphate is used to make the acyl phosphate intermediate. While the yields from the other two catalyzed reactions were only moderately good, which is probably a reflection of improper stoichiometry owing to incomplete formation of the enol phosphate, they were still significantly higher than the yield obtained from the uncatalyzed process. From the standpoint of triglyceride syntheses, however, the most important feature of this study is the degree of product specificity which was achieved by the use of perchloric acid. The noncatalyzed reaction gave a mixture of 57% 2-oleoyl 1,3-dipalmitin and 43% 3-oleoyl 1,2-dipalmitin. This product distribution corresponds closely to that which would be expected if an equilibrium mixture of 1,3- and 1,2-dipalmitins were acylated.[10,11] In contrast to the noncatalyzed reaction, all of the esterifications which employed perchloric acid catalysis were highly specific and gave triglycerides consisting of approximately 90%[12] of unisomerized product. In this respect there is little difference between acyl phosphates and anhydrides.

The question of whether or not acyl phosphates offer any improvements over carboxylic acid anhydrides as intermediates in the synthesis of nonrandom triglycerides would depend upon the specific examples in question. The phosphate route does employ the carboxylic acid twice as efficiently and does give a more easily purified product. Both of these considerations would be of particular importance if the carboxylic acid were especially valuable or especially hard to remove or recover. Admittedly, however, for most normal situations, the advantages to be gained by using an acyl phosphate would be balanced to a large degree by the greater ease with which an anhydride could be prepared.

(10) It has recently been proposed[11] that an equilibrium mixture of diglycerides contains about 84% of the 1,3 and 16% of the 1,2 isomer rather than the more widely accepted 60:40 distribution. The present results, while neither proving nor disproving either of these values, are more in agreement with the latter.

(11) H. J. Harwood, A. E. Thomas, III, J. E. Scharoun, and R. Slutkin, *Chem. Ind.* (London), 651 (1963).

(12) Isomerically pure diglycerides are difficult to prepare and the 1,3-dipalmitin may have contained a few per cent of the 1,2 isomer. It is therefore possible that the extent of isomerization was even less than the results indicate.

TABLE II

ESTERIFICATION OF 1,3-DIPALMITIN WITH DIETHYL OLEOYL PHOSPHATE

Reaction	Yield, g.	Anal. A.v.	Anal. H.v.	Anal. I.v.[a]	Product composition, % Oleic acid (a.v. = 198)	Product composition, % Dipalmitin (h.v. = 99)	Product composition, % Oleoyl dipalmitin	Yield of oleoyl dipalmitin, %
I	16.0[b]	4.9	31.5	20.7	2.5	31.8	65.7	51
II	17.7[b]	1.8	6.3	26.5	0.9	6.4	92.7	79
III	16.4[b]	3.2	0	28.7	1.6	0	98.4	78
IV	77.8[c]	3.5	0	31.0	1.8	0	98.2	92

[a] Iodine value of oleoyl dipalmitin, 30.6. [b] Theoretical yield of oleoyl dipalmitin, 20.8 g. [c] Theoretical yield of oleoyl dipalmitin, 83.2 g.

Experimental Section

2-Carbalkoxy-1-alkoxyvinyl Dialkyl Phosphates.—The procedure reported by Cramer and Gärtner[2a] was followed. Under an atmosphere of argon, a solution of the trialkyl phosphite in 2 vol. of ether was added dropwise to a stirred solution of an equimolar amount of the dialkyl bromomalonate, also dissolved in 2 vol. of ether. The reaction temperature was maintained at 0–5° by means of an ice bath. After the addition had been completed, the reaction mixture was stirred for 30 min., and the ether and other volatiles were then removed under vacuum. Rapid vacuum distillation of the residue gave the enol phosphate.

A. 2-Carbethoxy-1-ethoxyvinyl Diethyl Phosphate (I).—From 33.2 g. (0.20 mole) of triethyl phosphite and 47.8 g. (0.20 mole) of diethyl bromomalonate there was obtained 47.3 g. (80%) of I, b.p. 120–124° (0.3 mm.), $n^{25}D$ 1.4496 (lit.[2a] $n^{25}D$ 1.4513).

Anal. Calcd. for $C_{11}H_{21}O_7P$: P, 10.5. Found: P, 11.0.

B. 2-Carbomethoxy-1-methoxyvinyl Dimethyl Phosphate (II).—The reaction of 55.8 g. (0.45 mole) of trimethyl phosphite and 95.0 g. (0.45 mole) of dimethyl bromomalonate gave 85.0 g. (79%) of II, b.p. 135–140° (0.4–0.6 mm.), $n^{25}D$ 1.4588.

Anal. Calcd. for $C_7H_{13}O_7P$: P, 12.9. Found: P, 12.8.

C. 2-Carbethoxy-1-ethoxy-1-propenyl Diethyl Phosphate (III).—From 35.6 g. (0.21 mole) of triethyl phosphite and 54.3 g. (0.21 mole) of diethyl 2-bromo-2-methylmalonate was obtained 55.2 g. (85%) of III, b.p. 123–127° (0.4 mm.), $n^{25}D$ 1.4401.

Anal. Calcd. for $C_{12}H_{23}O_7P$: P, 10.0. Found: P, 10.1.

Triethyl Phosphonoacetate.—This phosphonate was prepared by means of the Michaelis–Arbuzov reaction.[13] A mixture of 123 g. (1.0 mole) of ethyl chloroacetate and 166 g. (1.0 mole) of triethyl phosphite was heated at 128–140° for 4 hr. Distillation of the product gave 150 g. (67%) of triethyl phosphonoacetate, b.p. 80–82 (0.25 mm.), $n^{25}D$ 1.4301 (lit.[14] $n^{25}D$ 1.4310).

Tetraethyl Phosphonomalonate (IV).—A 53.4% suspension of sodium hydride in mineral oil (4.5 g., 2.4 g. of NaH, 0.10 mole) was washed three times with dry benzene under argon. After the final wash, an additional 200 ml. of dry benzene was added as the reaction solvent. This mixture was cooled slightly and 22.4 g. (0.10 mole) of triethyl phosphonoacetate was added. The temperature was kept below 20° during addition of the phosphonate. The resulting mixture was stirred for 20 min. at room temperature and then 10.8 g. (0.10 mole) of ethyl chloroformate was added dropwise at 25–30°. After a 15-min. reaction time, the benzene solution was poured into water, the layers were separated, and the aqueous layer was extracted several times with chloroform. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvents were evaporated. Distillation of the residue gave 2.8 g. (9%) of tetraethyl phosphonomalonate, b.p. 127° (0.5 mm.).

The phosphonate fractions from several such reactions were combined and distilled through a spinning-band column to give an analytical sample, b.p. 109–110° (0.2 mm.), $n^{25}D$ 1.4371 [lit.[15] b.p. 155° (3 mm.)].

Anal. Calcd. for $C_{11}H_{21}O_7P$: P, 10.5. Found: P, 10.5.

Reaction of Triethyl Phosphite and Diethyl Bromomalonate at Elevated Temperature.—The procedure reported by Kosolapoff[2a] was followed. The reaction was carried out in a flask equipped with a stirrer, a condenser, and an addition funnel. A nitrogen atmosphere was maintained in the flask during the reaction. Triethyl phosphite (33.2 g., 0.20 mole) was added dropwise to 47.8 g. (0.20 mole) of diethyl bromomalonate contained in the flask. Care was taken that the reaction did not become excessively violent but no effort was made, beyond that, to control the temperature. After addition of the phosphite, the reaction mixture was heated for 4 hr. at 150°.

The infrared, P^{31}, and H^1 spectra of the crude reaction mixture were essentially the same as corresponding spectra of 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I) prepared at 0° in ether. No P^{31} resonance at −12.8 p.p.m. (tetraethyl phosphonomalonate) could be detected.

Vacuum distillation of the reaction mixture gave 38.0 g. (64%) of a product, b.p. 100–130° (0.1 mm.), $n^{25}D$ 1.4394. The P^{31} spectrum of this product contained a band at +12.6 p.p.m. (tetraethyl pyrophosphate) in addition to the band at +8.9 p.p.m. Otherwise, its spectra were identical with those of I.

Tripalmitin.—A 5-l., three-necked flask, fitted with a mechanical stirrer and a thermometer, was connected through Dry Ice cooled traps to a vacuum pump. Methyl palmitate (621 g., 2.3 moles) was added to the flask and heated to 140° under vacuum. Then 65.8 g. (0.67 mole of glycerol) of a solution of 5.5 g. of sodium hydroxide in 90 g. of dry glycerol was added, the flask was again evacuated, and the temperature was slowly raised to 180° and held there for 5 hr. The resulting tripalmitin was used without isolation for the preparation of 1,3-dipalmitin.

1,3-Dipalmitin.—The method of Baur and Lange[16] for the directed rearrangement of triglycerides to 1,3-diglycerides was used with some modification. The above tripalmitin, which had cooled and solidified, was remelted. Triacetin (293 g., 1.34 moles) and 15 ml. of a 10% suspension of sodium methoxide in xylene were then added and the reaction temperature was adjusted to 60°. Dry glycerol (99 g., 1.08 moles) was added and this mixture was stirred at 60° for 3 hr. The entire process was carried out under a stream of nitrogen. The mixture was then allowed to cool slowly to 50° at which time it was transferred to a screw-cap jar and stored at 21° for 2 days.

The resulting solid mass was dissolved in approximately 10 vol. of a 1:1 hexane–ethanol solution, 10 ml. of glacial acetic acid was added to inactivate the sodium methoxide catalyst, and the material was recrystallized at 21°. The precipitate was redissolved in 1500 ml. of chloroform and water washed until the aqueous washings were neutral to litmus paper. The chloroform solution was dried over anhydrous magnesium sulfate and filtered, and most of the chloroform was evaporated. Two additional recrystallizations from 10 vol. of 1:1 hexane–ethanol solution gave 306 g. (0.54 mole, 80% based on 0.67 mole of tripalmitin) of 1,3-dipalmitin.

Anal. Calcd. for $C_{35}H_{68}O_5$: hydroxyl value (h.v.), 99; saponification value (s.v.), 197; acid value (a.v.), 0. Found: h.v., 99; s.v., 195; a.v., 0.

Esterification of 1,3-Dipalmitin.—The acylating intermediate, diethyl oleoyl phosphate, was prepared by combining equimolar amounts of 2-carbethoxy-1-ethoxyvinyl diethyl phosphate (I) and oleic acid (99+% purity) at room temperature. The reactants were stirred in a round-bottomed flask under nitrogen until the strong vinyl group infrared absorption of the enol phosphate (1647 $cm.^{-1}$) had disappeared. When the enol phosphate had not been purified before use, the reaction was usually complete after stirring overnight, but freshly distilled enol phosphate required as much as 6 days to react with oleic acid. The resulting acyl phosphate was used directly for the esterification reactions.

The data obtained from four reactions of diethyl oleoyl phosphate with 1,3-dipalmitin are listed in Table II. The acyl

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phosphate used in each of reactions I–III was prepared from 11.2 g. (0.038 mole) of a sample of freshly prepared but undistilled enol phosphate and 10.7 g. (0.038 mole) of oleic acid. Reaction IV employed 44.4 g. (0.15 mole) of distilled enol phosphate and 42.3 g. (0.15 mole) of oleic acid. The following experimental conditions were used for the acyl phosphate–dipalmitin reactions.

Reaction I.—1,3-Dipalmitin (14.2 g., 0.025 mole) and 300 ml. of water-washed, dried, and distilled (alcohol-free) chloroform were added to the acyl phosphate, and this mixture was stirred overnight under argon at room temperature.

Reaction II.—To a solution of 300 ml. of alcohol-free chloroform, the acyl phosphate, and 14.2 g. (0.025 mole) of 1,3-dipalmitin was added 0.050 ml. of 70% perchloric acid. The reaction mixture was stirred in an argon atmosphere for 3.5 hr. at room temperature.

Reaction III.—A solution of the acyl phosphate in 300 ml. of alcohol-free chloroform was preheated to 50°, and then 14.2 g. (0.025 mole) of 1,3-dipalmitin and, finally, 0.050 ml. of 70% perchloric acid were added. This solution was kept under argon for 3.5 hr. at 50°.

Reaction IV.—A solution of the acyl phosphate, 56.9 g. (0.10 mole) of 1,3-dipalmitin, and 0.257 ml. of 70% perchloric acid in 500 ml. of alcohol-free chloroform was stirred at room temperature for 4 hr. under argon.

All of the products were isolated in the same manner. The chloroform solution was poured into an equal volume of water in a separatory funnel. Enough ether was added to give a lighter-than-water organic layer which was then water washed three times. The organic layer was dried over anhydrous magnesium sulfate and filtered, and most of the solvent was evaporated. The residual solid was dissolved in approximately 10 vol. of acetone and recrystallized at −7° to give the products whose analyses are listed in Table II.

These triglycerides were then freed of fatty acid and diglyceride by column chromatography (4-g. sample on a 40-g. silica gel with 5% water column eluted with 500 ml. of benzene), and the 2-position fatty acids of the pure triglycerides were determined by the lipase hydrolysis method of Mattson and Volpenhein.[9] The results are shown in Table I.

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Reaction of Enamines with Nitro Olefins[1]

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The morpholine enamines of cyclohexanone, cyclopentanone, desoxybenzoin, and 2-methylcyclohexanone reacted with nitroethylene and 2-acetoxynitroethane to give aminocyclobutanes or alkylated enamines. The corresponding nitroethyl ketones were formed on acid hydrolysis. Reactions of the first three enamines and of the pyrrolidine enamine of butyraldehyde with nitrostyrene gave similar condensation products. Factors affecting the course of these reactions are discussed.

Ketones bearing a γ-nitrogen substituent are of interest as synthetic intermediates for hydroindoles and thus are useful in synthetic schemes leading to many structurally diverse natural products such as alkaloids of the aspidosperma, amaryllidacea, and erythrina classes. One approach to their preparation has been the substitution of ketones with a β-nitroethyl group, using the Mannich condensation. Although 2-dimethylaminomethylcyclohexanone was reported to react with nitromethane and sodium methoxide to give nitroethylcyclohexanone in 72% yield,[3] the sequence appeared to be of limited use in the hands of other investigators who found that this reaction furnished only 15% of the pure product.[4] Through a more extensive route using nitrodiethyl malonate in the Mannich condensation, followed by ester hydrolysis and decarboxylation, the over-all yield of nitroethylcyclohexanone could be raised to 40%.[4a]

The present report describes the direct nitroethylation of ketones and aldehydes in form of their enamine derivatives with nitroethylene, β-acetoxynitroethane, and nitrostyrene as alkylating agents.

A vigorous exothermic reaction was seen on addition of nitroethylene to morpholinocyclohexene (Ia). The course of this reaction was found to depend upon the polarity of the solvent. In acetonitrile, at −20°, the main product was an alkylated enamine IIa, whereas in a hydrocarbon solvent the reaction led primarily to an aminocyclobutane IIIa. Storage of either product at room temperature for a few hours in the original solvents or in the interchanged solvents did not result in noticeable interconversion of the aminocyclobutane and alkylated enamine. Even in refluxing acetonitrile the aminocyclobutane product did not undergo ring cleavage to the alkylated enamine. These results indicate that the two products do not arise from equilibration and that their formation must be considered to be kinetically controlled. In accord with these observations, one can postulate a zwitterionic reaction stage IV which collapses rapidly to the aminocyclobutane III in a nonpolar solvent but in polar solvents has an expected increased lifetime and selectivity for further transformations. This selectivity is expressed in the proton transfer which leads to an enamine product II. Abstraction of a proton from the α′ side of the α-substituted cycloheximmonium intermediate through a six-membered transition state is preferred[5] and could be established by showing the presence of a vinyl enamine hydrogen in the n.m.r. spectrum of the product.

Hydrolysis of the aminocyclobutane IIIa or the alkylated enamine IIa with acid (through protonated IV) gave nitroethylcyclohexanone Va in 80% yield.

The enamine alkylation method[6,7] is particularly

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(2) National Science Foundation undergraduate research participant.

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(5) The assignment of this reaction pathway is also in accord with other reactions of enamines with electrophiles which lead to dipolar intermediates where selectivity in further transformations could be demonstrated and controlled by structural variations. To be published.

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