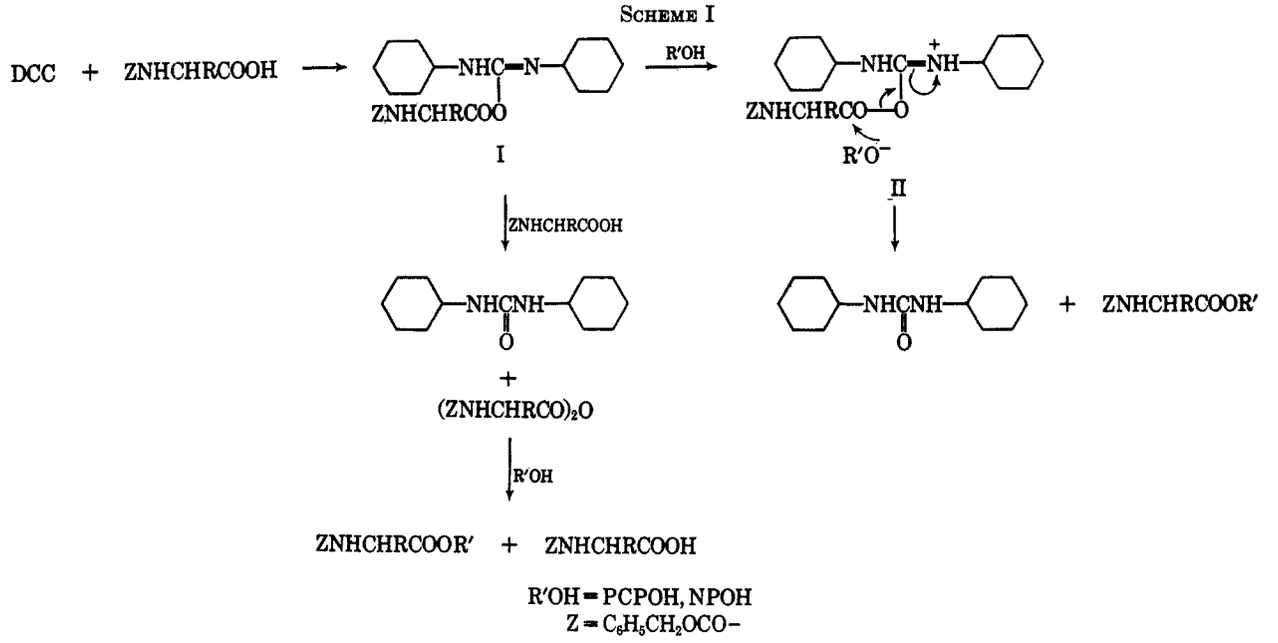
SCHEME I



R'OH = PCPOH, NPOH
Z = $C_6H_5CH_2OCO-$

acetate (25 ml), diluted with petroleum ether (400 ml), and refrigerated overnight. Filtration and washing three times with 100-ml portions of petroleum ether–ethyl acetate (10:1) and then cold ether (50 ml) yielded 61.8% crude ester, mp 176–181°. Recrystallization from ethanol gave the raised mp 189–190°, yield 50%; another recrystallization from ethyl acetate gave the analytical sample, mp 191.5–192.5°.

N-Carbobenzoxynitro-L-arginine PCPOH Ester.—To a solution of N-carbobenzoxynitro-L-arginine[24] (2.0 g, 5.67 mmoles) and PCPOH (4.5 g, 17 mmoles) in dimethylformamide (10 ml), DCC (1.17 g, 5.67 mmoles) was added. Stirring was continued at room temperature for 2 hr. The mixture was then cooled to −10°, filtered, and the filtrate poured into water (300 ml). The resulting oil crystallized on trituration with water. The product was suspended in ether, diluted with petroleum ether, filtered, and washed with ether. Recrystallization from tetrahydrofuran–ether gave 2.50 g (73.5%), mp 102–105°. One more recrystallization from the same solvent gave the raised mp 109–111.5°, yield 68%. A sample was recrystallized once more for analysis.

Anal. Calcd for $C_{20}H_{18}N_5O_6Cl_5$: C, 39.92; H, 3.02; N, 11.64; Cl, 29.46. Found: C, 40.09; H, 3.44; N, 11.79; Cl, 29.44.

When a crude sample was recrystallized from dimethylformamide–ether the ester was solvated with 1 mole of dimethylformamide, mp 109.5–111°.

Anal. Calcd for $C_{20}H_{18}N_5O_6Cl_5 \cdot C_3H_7NO$: C, 40.94; H, 3.73; N, 12.46; Cl, 26.27. Found: C, 40.41; H, 3.61; N, 12.21; Cl, 26.48.

The solvated dimethylformamide was removed by two procedures: (a) trituration with water and then anhydrous ether, mp 105–110°, and (b) recrystallization from tetrahydrofuran–ether, mp 108.5–111°.

N-Carbobenzoxy-α-*t*-butyl-L-glutamate PCPOH Ester.—To a cold (0°) stirred solution of N-carbobenzoxy-α-*t*-butyl-L-glutamate[25] (7.0 g, 21 mmoles) in methylene chloride (140 ml), DCC (4.3 g, 21 mmoles) was added, followed after 5 min by PCPOH (5.6 g, 21 mmoles). Stirring was continued in the cold for 30 min and at room temperature for 5 hr. Glacial acetic acid (1 ml) was added and stirring continued for 30 min. The mixture was filtered, the precipitate (DCU) washed with methylene chloride (25 ml), and the filtrate concentrated under vacuum. The solid residue was recrystallized from methanol: yield 7.4 g (62%); mp 122–124°.

Registry No.—PCPOH ester of Z-Leu, 13758-71-9; PCPOH ester of Z-Val, 4824-13-9; PCPOH ester of Z-Met, 4841-70-7; PCPOH ester of Z-Try, 13673-49-9; PCPOH ester of Z-Cys-Cys-Z, 13673-50-2; PCPOH ester of Z-Glu-NH_2, 13673-51-3; PCPOH ester of Z-Lys-Z, 13673-52-4; PCPOH ester of Z-Ileu, 13673-53-5; PCPOH ester of Z-Cys-BZL, 13673-54-6; PCPOH ester of Z-γ-Abut, 13673-55-7; PCPOH ester of Z-Pro, 13673-56-8; PCPOH ester of Z-Ser, 13673-57-9; PCPOH ester of Z-Arg-NO_2, 5165-16-2; PCPOH ester of Z-Glu-OBu-*t*, 6233-91-6.

Acknowledgment.—This work was supported by grants from the National Institutes of Health, Public Health Service (GM 06579 and 08795). We wish to thank Professor H. Horan for the infrared spectra.

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Plasmalogen Synthesis. Use of 1-Alkynylglycerols and the Production of Allenic Ethers[1a]

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Received March 22, 1967

Attempts to synthesize plasmalogens have been recently reported from several laboratories.[3-8] An apparently convenient synthetic route to 1-alkenyl ethers of isopropylideneglycerol through the corresponding acetylenic ethers as intermediates was re-

(1) (a) Abstracted from a part of the dissertation submitted by G. K. Chacko to the University of Illinois Graduate College in partial fulfillment of the requirements of the Ph.D. degree. (b) Visiting Professor from Denmark Tekniske Hojskole, Kemisk Laboratorium B, Lyngby, Denmark. Supported by Training Grant USPH 5368.

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ported by a group of Russian workers.[9] This route would allow control over the configuration of the double bond formed from the partial hydrogenation of the triple bond. Furthermore, this would permit the preparation of plasmalogen derivatives of the desired optical configuration. In addition, these workers reported the preparation of 1-O-hept-1′-enyl-2,3-O-isoproplideneglycerol by partial hydrogenation of the product obtained by condensation of the sodio derivative of isopropylideneglycerol with 1-bromohept-1′-yne. In the present communication, results of studies directed toward the synthesis of plasmalogens using the above method are reported.

Using the procedure reported for the synthesis of l-O-hept-1′-ynyl-2,3-O-isopropylideneglycerol,[9] the preparation of 1-O-hexadec-1′-ynyl-2,3-O-isopropylideneglycerol was attempted by the condensation of 1-bromohexadec-1′-yne with the sodio derivative of 2,3-O-isopropylideneglycerol. The 1-bromohexadec-1′-yne was prepared from 1-hexadec-1′-yne following the procedure reported for the synthesis of 1-bromoheptyne.[10] The infrared spectrum of the condensation product, the deacetonated glycerol ether, and its diacyl derivatives showed a fairly strong absorption at 1965 cm^{-1}, generally ascribed to the allene chromophore,[11] and did not show the anticipated characteristic absorption for acetylenic ether[5] in the region 2100–2300 cm^{-1}. Surprisingly, when the 1-O-hept-1′-ynyl-2,3-O-isopropylideneglycerol was prepared according to the published procedure and its infrared spectrum determined, it also showed a strong absorption band at 1965 cm^{-1} and no peak in the expected region of 2100–2300 cm^{-1}. In order to compare the infrared absorption of acetylenic ethers, 1-methoxy-1′ heptyne was synthesized according to the method of Nooi and Arens.[12] This authentic acetylenic ether showed absorption at 2300 cm^{-1} for the triple bond and no absorption near 1965 cm^{-1}.

Furthermore, the condensation product of 1-bromo-1′-alkyne with the sodio derivative of isopropylideneglycerol, presumably an allenic ether, was found to react with iodine in methanol to form an α,β-unsaturated α-iodoaldehyde (2-iodohept-2-enal in the present experiments) and not an iodo acetal which was reported to result from the reaction of iodine in methanol with vinylic ethers.[13] When 1-O-hept-1′-2′-dienyl-2,3-O-isopropylideneglycerol in methanol was treated with iodine solution, it was found to react rapidly and produce an immiscible brown oily liquid, which was recovered by extraction with ether. The same product was found when the reaction was carried out in the absence of methanol, indicating that methanol was not a reagent as in the case of the reaction of iodine with vinyl ethers.[13] The infrared spectrum of the product had a strong carbonyl peak at 1710 cm^{-1} and another strong peak at 1610 cm^{-1}, presumably due to a conjugated double bond. There was also a peak at 2750 cm^{-1}, the CH stretching vibration of an aldehyde group.

The aldehyde nature of the product was further confirmed when treatment with Fuchsin aldehyde reagent[14] caused an immediate positive reaction. Furthermore, an immediate precipitation occurred with 2,4-dinitrophenylhydrazine (DNP) reagent and the DNP derivative melted sharply at 172–173° and had a λ_{max} 372 mμ (ϵ_{max} 28,000), a shift to higher wavelength when compared with the DNP derivative of a nonconjugated aldehyde.[15]

Under alkaline conditions, acetylenic compounds may isomerize to an equilibrium mixture of the corresponding allenic derivatives. In the preparation of acetylenic ethers, this may occur either before or after the formation of the ether. To test these possibilities, 1-methoxy-1′-heptyne, prepared according to the method of Nooi and Arens,[12] was refluxed with sodium alkoxide for various intervals of time, a condition used for the attempted preparation of acetylenic ethers; the isolated product still retained the strong acetylenic ether peak in the infrared region and no allenic ether absorption appeared near 1965 cm^{-1}. The most probable course of reaction thus seems to be the formation of 1-bromo-1′,2′-alkadiene by rearrangement of the 1-bromo-1′-alkyne. If we assume that the former reacts with alkoxide much faster than the latter, the final product would be predominantly an allenic ether rather than the expected acetylenic ether. Therefore, the results reported by Berezovskaya, *et al.*,[9] describing the synthesis of a vinyl ether of isopropylideneglycerol seem to be open to doubt.

Experimental Section

The infrared spectra were determined on a Beckman Model 7 spectrophotometer. Melting and boiling points are not corrected. All indices of refraction were measured on a Zeiss refractometer. Microanalyses were carried out by the Clark Microanalytical Laboratories, Urbana, Ill.

1-Bromohept-1′-yne and 1-Bromohexadec-1′-yne.—1-Bromohept-1′-yne (1) was prepared from 1-heptyne by the procedure of McCusker and Voit:[10] yield, 63%; bp 42–42.5° (4 mm) (lit.[10] bp 69° (25 mm); $n^{21}D$ 1.4672 (lit.[10] $n^{22}D$ 1.4678).

Anal. Calcd for $C_7H_{11}Br$: C, 48.00; H, 6.28; Br, 45.72. Found: C, 48.12; H, 6.23; Br, 45.66.

1-Bromohexadec-1′-yne (2) was made from 1-hexadecyne in a manner similar to that of 1-bromohept-1′-yne except that a more dilute ethereal solution of alkynylmagnesium bromide was used. (1-Hexadecyne was made by dehydrobromination of 1,2-dibromohexadecane with sodium amide in anhydrous toluene.[16]) The yield of 2 was 66%: bp 118.5–119° (0.1 mm); $n^{21.5}D$ 1.4735.

Anal. Calcd for $C_{16}H_{29}Br$: C, 63.80; H, 9.60; Br, 26.6. Found: C, 63.62; H, 9.74; Br, 26.7.

Attempted Preparation of 1-O-Hept-1′-ynyl-2,3-O-isopropylideneglycerol (3).—The preparation of 3 was attempted according to the procedure of Berezovskaya, *et al.*,[9] and resulted in a product with the following characteristics: yield, 23%; bp 72–73° (0.25 mm); $n^{23}D$ 1.4585; ν_{max}^{smear} 1960 cm^{-1} (lit.[9] bp 69–70° (0.5 mm); $n^{20}D$ 1.4580.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.02, H, 9.73. Found: C, 68.90; H, 9.80.

Attempted Preparation of 1-O-Hexadec-1′-ynyl-2,3-O-isopropylideneglycerol (4).—Synthesis of 4 was attempted according to the procedure of Berezovskaya, *et al.*,[9] and a product similar to the above C_7 analog was obtained in a yield of 13% after silicic acid column chromatography.

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Anal. Calcd for $C_{22}H_{40}O_3$: C, 75.01; H, 11.3. Found: C, 74.72; H, 11.1.

1-O-Hexadec-1′,2′-dienylglycerol (5).—Crude product **4** (4 g, 11.3 mmoles) was hydrolyzed with[17] 6.2 g (40 mmoles) of finely powdered boric acid in 20 ml of methyl cellosolve in a boiling water bath for 1 hr. The residue was dissolved in Skellysolve F and cooled at −10°F overnight to yield a yellow precipitate. This was collected by filtration in the cold to obtain 0.357 g of **5** in 10% yield: $n^{24.5}D$ 1.4727; ν_{max}^{smear} 1965 (OC=C=C–), 3420 cm^{-1} (OH).

Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.08; H, 11.54. Found: C, 72.93; H, 11.26.

1-O-Hexadec-1′,2′-dienyl-2,3-di-O-palmitoylglycerol (**6**) was prepared by acylation of **5** (0.4 g, 1.25 mmoles) with palmitoyl chloride (1.05 g, 3.8 mmoles) in the presnce of 8 ml of pyridine and in 20 ml of dry $CHCl_3$. The product (**6**) was obtained by recrystallization from acetone at 0°: yield, 89%; mp 38–39°; ν_{max}^{smear} 1755 (ester C=O), 1950 cm^{-1} (OC=C=C).

Anal. Calcd for $C_{51}H_{96}O_5$: C, 77.67; H, 12.18. Found: C, 77.67, H, 12.32.

1-O-Hexadec-1′,2′-dienyl-2,3-di-O-oleylglycerol was prepared as outlined above and obtained as an oil in 60% yield: ν_{max}^{smear} 1760 (ester C=O), 1970 cm^{-1} (-OC=C=C).

Anal. Calcd for $C_{55}H_{100}O_5$: C, 78.56; H, 11.91. Found: C, 78.63; H, 11.90.

Reaction of Iodine with 1-O-Hept-1′,2′-dienyl-2,3-O-isopropylideneglycerol.—To a solution of 1-O-hept-1′,2′-dienyl-2,3-O-isopropylideneglycerol in methanol was added 0.1 *N* iodine solution until there was a permanent yellow color. The immiscible yellow liquid which separated was recovered by ether extraction: ν_{max}^{smear} 1710 (aldehyde C=O), 1610 (conjugated C=C), 27.50 cm^{-1} (CH stretching of aldehyde); orange-red 2,4-dinitrophenylhydrazone derivative had mp 172–173° dec; λ_{max}^{EtOH} 372 mμ (ϵ_{max} 28,000).

Anal. Calcd for $C_{13}H_{15}N_4O_4I$: C, 37.32; H, 3.59; N, 13.40; I, 30.3. Found: C, 37.30; H, 3.69; N, 13.26; I, 29.10.

Registry No.—**2**, 13866-75-6; **3**, 13866-76-7; **5**, 13866-77-8; **6**, 13866-78-9; 1-O-hexadec-1′,2′-dienyl-2,3-di-O-oleylglycerol, 13970-35-9.

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Enolization of Ketones. III.[1] The Rate and Orientation of Acid-Catalyzed Deuteration of Some Methyl Ketones

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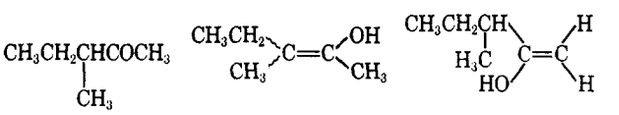
The acid-catalyzed enolization of ketones has been studied by means of halogenation, racemization of optically active ketones, and deuteration experiments.[2-9] Of these methods, halogenation has been most commonly used.

In 1935, Bartlett and Stauffer studied the acid-catalyzed enolization of some secondary butyl ketones.[6] From a comparison between the rate of racemization of the optically active ketones and their over-all rate of iodination, the rate of reaction at each of the α carbons and the orientation of substitution were calculated. Bartlett and Stauffer found no general rules for the orientation of substitution.[6]

In 1951, Cardwell and Kilner studied the orientation of the enolization of a number of ketones by halogenation experiments.[8] From a comparison with the rate of iodination for the same ketones determined by Dawson,[10] the relative rate of halogenation of each of the two α carbons could be calculated. The orientation was found to follow the Saytzeff rule and this investigation has been considered as a classic investigation of the orientation of enolization as well as of hyperconjugation.[8,11]

3-Methyl-2-pentanone (I) was studied in both investigations. Bartlett and Stauffer reported a value



I II III

for the orientation of enolization, "3-enol"/"1-enol" = II/III = 0.22, while Cardwell and Kilner found the same ratio (II/III) to be 3.8.[6,8] Cardwell and Kilner explained the large difference to be due to the use of very incompletely resolved ketone in the racemization experiment.[8] However, in our opinion it is difficult to see how this could influence the rate of racemization and therefore the reason for the discrepancy must be found elsewhere.

In the halogenation experiments, the separation of the two α-monohalo isomers and the polyhalo ketones was made by distillation and, as already pointed out by Cardwell and Kilner, it is difficult to estimate the accuracy of these analyses. Another objection that can be raised against these results is that rearrangements can occur during the syntheses and the long distillations of the halogenated ketones.[12]

Nmr spectroscopy has proven to be an excellent tool with which to follow the deuteration of ketones. Here the orientation and the rate of reaction can be estimated in the same experiment.[13,14] In a recent paper, one of us studied the orientation of deuteration in 2-butanone in both acid- and base-catalyzed reactions. In the case of acid-catalyzed reactions, the orientation of deuteration was found to be approximately the same as the orientation of halogenation.[13,15]

Later, Bothner-By and Sun, who used the same nmr technique, confirmed the orientation for the acid- and base-catalyzed deuteration of 2-butanone.[16] In addition to 2-butanone, these authors also studied the deuteration of acetone, 3-pentanone, and methoxyacetone. Since 3-pentanone was found to enolize more slowly

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