Studies Directed toward the Synthesis of Plasmalogens.
I. Alkenylglycerols[1]

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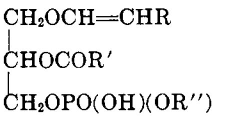
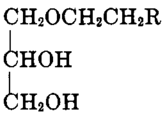
Debromination of the glycerol α-bromo cyclic acetals (IVa and IVb) by means of lithium in dimethoxyethane afforded alkenyl ethers which were shown by infrared and n.m.r. spectroscopy, vapor phase chromatography, and periodate titration to consist of a mixture of the *cis*- and *trans*-1-alkenyl- (III) and the *cis*- and *trans*-2-alkenylglycerols (V) in the ratio of approximately 47:53, and of total *cis* to total *trans* compounds in the ratio of 4:5.

Plasmalogens are a group of aldehydogenic substances widely distributed in nature in both the animal and plant kingdom.[2] Their chemical structure is that of a *cis*-α-alkenyl ether of a glyceryl phosphate (I) where R″ may be derived from choline, ethanolamine, or serine. Hydrogenation and acid hydrolysis yielded[3a] chimyl and batyl alcohols (IIb and IIc), while enzymic hydrolysis followed by alkaline saponification afforded a *cis*-1-alkenylglycerol (III), the fatty aldehydes from which were shown[3] to be almost completely saturated and to consist mainly of the palmitic and stearic derivatives. The 1-alkenylglycerols (IIIb and IIIc) are therefore of considerable chemical and biological interest, particularly in view of their possible biogenetic relationship[4] to the corresponding hemiacetals (which could be formed by a facile hydration of the double bond), and thence (by a mild oxidation[4]) to the 1-acylglycerols. We now report the results of experiments directed towards the synthesis of the 1-alkenylglycerols (III).



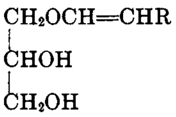
$$\begin{array}{l} CH_2OCH{=}CHR \\ | \\ CHOCOR' \\ | \\ CH_2OPO(OH)(OR'') \end{array}$$

I



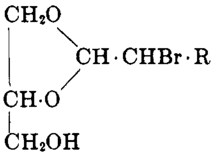
$$\begin{array}{l} CH_2OCH_2CH_2R \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

II

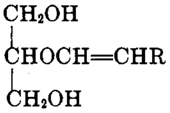


$$\begin{array}{l} CH_2OCH{=}CHR \\ | \\ CHOH \\ | \\ CH_2OH \end{array}$$

III



IV



$$\begin{array}{l} CH_2OH \\ | \\ CHOCH{=}CHR \\ | \\ CH_2OH \end{array}$$

V

The application of the Wittig reaction[5] to VI, followed by condensation of the ylid with the aldehyde R·CHO, should lead to the 1-alkenylglycerol (III). As a model compound, the known[6] 4-(chloromethoxymethyl)-1,3-dioxolane (VII) was examined. Reaction with triphenylphosphine gave the hygroscopic phosphonium chloride, which was converted to the stable iodide (VIII, X = I). Distillation of VIII with methanolic hydrochloric acid caused elimination of formaldehyde as dimethylformal, and left the phosphonium salt (IX, X = Cl) as a viscous sirup, which was converted to the crystalline iodide (IX, X = I). However, the ylid from VIII, whether prepared by use of sodium methoxide, potassium *t*-butoxide, phenyllithium or butyllithium, could not be induced to condense with dodecanal, and this route was therefore abandoned in view of the encouraging results obtained in an alternative approach.

A second possible pathway toward the 1-alkenylglycerol (III) is offered by the debromination[7,8] of an α-bromoglycerol acetal (IV), and we now report an investigation of this route for the preparation of the model compound (IIIa, R = *n*-decyl) and the parent substance (IIIb, R = *n*-tetradecyl).

In both cases the aldehyde was converted to the enol acetate which was brominated in carbon tetrachloride and then treated with anhydrous methanol to yield the α-bromodimethyl acetal.[9] A *trans*-acetalation reaction[10] with glycerol was utilized to produce the 2-(α-bromo-*n*-undecyl)- and 2-(α-bromo-*n*-pentadecyl)-4-hydroxymethyl-1,3-dioxolanes (IVa and IVb).

A similar reaction with α-monotritylglycerol[11] was carried out in order to obtain the α-trityl ether of IVa, but the reaction product here was also IVa itself, with triphenylmethanol as by-product.

The dehalogenation of α-halo ethers to give α-alkenyl ethers has been reported using sodium in boiling ether,[7,8] and, after the work described in this paper had been completed, this method of preparation was reported[7b] to give 1-alkenyl ethers of glycerol (III, R = ethyl to *n*-nonyl) which were indicated to be of the *trans* configuration. The action of magnesium on 2-bromoethyl-2-methyl-1,3-dioxolane[12] is another example of the same reaction.

In our hands, the use of lithium in 1,2-dimethoxyethane afforded the optimum results (highest yield, purest product) for the ring opening of IVa and IVb with formation of III, as shown by the strong infrared absorption of the products (doublet centered at 1665

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[1] This work was supported by Research Grant HE-5881 from the National Institutes of Health, U. S. Public Health Service.

[2] For comprehensive reviews, see (a) E. Klenk and H. Debuch in "Progress in the Chemistry of Fats and Other Lipids," Vol. 6, Pergamon Press, Oxford, 1963; (b) M. M. Rapport and W. T. Norton, *Ann. Rev. Biochem.*, **31**, 103 (1962).

[3] (a) H. Debuch, *Z. physiol. Chem.*, **317**, 182 (1959); (b) E. L. Gottfried and M. M. Rapport, *J. Biol. Chem.*, **237**, 329 (1962); (c) G. M. Gray, *Biochem. J.*, **70**, 425 (1958); (d) S. J. Thannhauser, N. F. Boncoddo, and G. Schmidt, *J. Biol. Chem.*, **188**, 427 (1951).

[4] J. C. Craig and E. C. Horning, *J. Org. Chem.*, **26**, 2098 (1960).

[5] For review see: S. Trippett in "Advances in Organic Chemistry: Methods and Results," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1960.

[6] J. Lichtenberger and L. Martin, *Bull. soc. chim. France*, 468 (1947).

[7] (a) H. S. Hill and L. M. Pidgeon, *J. Am. Chem. Soc.*, **50**, 2718 (1928); H. S. Hill, *ibid.*, **50**, 2725 (1928). (b) C. Piantadosi, A. F. Hirsch, C. L. Yarbro, and C. E. Anderson, *J. Org. Chem.*, **28**, 2425 (1963).

[8] C. Piantadosi and A. F. Hirsch, *J. Pharm. Sci.*, **50**, 978 (1961).

[9] P. Z. Bedoukian, *J. Am. Chem. Soc.*, **79**, 889 (1957).

[10] C. Piantadosi, C. E. Anderson, E. A. Brecht, and C. L. Yarbro, *ibid.*, **80**, 6613 (1958).

[11] P. E. Verkade, J. Van der Lee, and W. Meerburg, *Rec. trav. chim.*, **54**, 716 (1935).

[12] J. F. Arens and D. A. van Dorp, *ibid.*, **65**, 729 (1946).

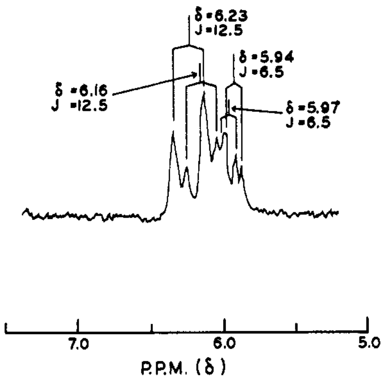


Figure 1.—N.m.r. spectrum showing the region corresponding to the olefinic proton adjacent to oxygen in the alkenylglycerol mixture obtained from the α-bromo cyclic acetal (IV).

cm.$^{-1}$) attributable[13] to the C=C stretching mode of the ether. It is known[13] that in this region *trans*-1-alkenyl ethers have a doublet; the *cis* isomers exhibit a single band only. In addition, both products absorbed at 927 and 734 cm.$^{-1}$ (the latter a shoulder on the long-chain methylene absorption band), characteristic[13] of *trans* and *cis* double bonds, respectively, suggesting that a mixture of *trans*- and *cis* alkenyl ethers had been formed in the reaction.

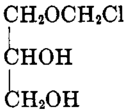
The n.m.r. spectra of *cis*- and *trans*-methyl 1-dodecenyl ether have been found[13b] to give a doublet corresponding to the olefinic proton adjacent to oxygen. The doublet of the *trans* compound has a coupling constant $J = 12.5$ c.p.s. and is shifted downfield relative to that of the *cis* isomer which has $J = 6.3$ c.p.s. From these results a mixture of *cis* and *trans* isomers of an alkenyl ether would be expected to present a pair of doublets with $J = 12.5$ and 6.3 c.p.s., respectively. However, the n.m.r. spectrum of both the 1-alkenyl ethers obtained from IVa and IVb had the pattern shown in Figure 1. This clearly demonstrates the existence of *two* pairs of doublets in this region with $J = 12.5$ and 6.5 c.p.s., respectively, suggesting that the dioxolane ring in IVa and IVb had opened in both possible ways during the debromination to give not only the *cis*- and *trans*-1-alkenylglycerols (IIIa and IIIb), but also their *cis*- and *trans*-2-alkenyl isomers (Va and Vb).

In an attempt to resolve this mixture, the product from the debromination of IVa was acetylated under anhydrous conditions, and the n.m.r. spectra of the acetylated and unacetylated products were shown to possess the same pattern for the olefinic proton adjacent to oxygen. Vapor phase chromatography of the acetylated material revealed it to consist of a mixture of two components A and B in the ratio of 4:5, and preparative v.p.c. furnished small amounts of A and B which had retention times of 26 and 33 min., respectively, and could be completely separated from each other. The infrared spectrum of A had bands at both 1664 and 734 cm.$^{-1}$, indicating it to be a *cis*-alkenyl ether. No detectable absorption was present at 927 cm.$^{-1}$. Fraction B however exhibited a broadened absorption band at 1660–1670 and a peak at 927 cm.$^{-1}$ (*trans*-alkenyl ether), but no detectable peak or shoulder at 734 cm.$^{-1}$. The n.m.r. spectra were in agreement with this interpretation, showing one pair of doublets in each case, with $J = 6.5$ c.p.s. in A, and 12.5 c.p.s. in B, respectively.

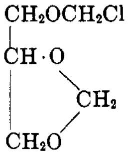
The above evidence confirms that debromination of IV produces a mixture of four compounds, *i.e.*, *cis*- and *trans*-III and *cis*- and *trans*-V, and that this mixture can be separated into two components: A (consisting of *cis*-III and *cis*-V) and B (made up of *trans*-III and *trans*-V). It is significant that the ratio of the retention times (t_{trans}/t_{cis}) is 1.27 for components A and B, in excellent agreement with that (1.29) found for the *cis*- and *trans*-methyl 1-dodecenyl ethers.[13b]

Further evidence for the composition of components A and B was afforded by catalytic hydrogenation, followed by hydrolysis, to yield the corresponding saturated diols which were then submitted to quantitative periodate oxidation[14] at pH 7.4 to determine the amount of 1,2-diol present in the mixture of 1,2- and 1,3-diols. Natural (+)-α-hexadecyl glycerol ether (chimyl alcohol) was used as a standard. By this means, it was found that the saturated diols derived from both components A and B contained 47 ± 3 mole % of 1,2-diol, indicating that ring opening of the dioxolane had indeed occurred in both directions to give a dodecenylglycerol mixture made up of the 1-alkenyl (III) and the 2-alkenyl moiety (V) in almost equal proportion.

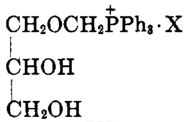
Repeated distillation of the alkenyl ether obtained from IVb gave a solid, m.p. 45–47°, which no longer showed absorption at 1666 cm.$^{-1}$ in the infrared spectrum, did not decolorize bromine solution, and lacked any olefinic protons in its n.m.r. spectrum. The compound was isomeric with the desired alkenyl ether, and gave the 2,4-dinitrophenylhydrazone of palmitaldehyde with Brady's reagent, consistent with its formulation as a cyclic acetal generated by the addition of one of the hydroxyl groups across the double bond of the alkenyl ether.


$CH_2OCH_2Cl-CHOH-CH_2OH$

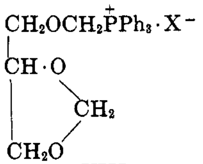
V



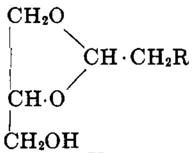
VII


$CH_2OCH_2\overset{+}{P}Ph_3\cdot X^- - CHOH - CH_2OH$

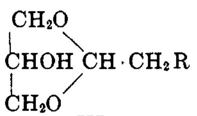
IX



VIII



X



XI

a, R = n-$C_{10}H_{21}$
b, R = n-$C_{14}H_{29}$
c, R = n-$C_{16}H_{33}$

The complex nature of the n.m.r. spectrum of the product did not permit a distinction to be made be-

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(13) (a) L. G. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958; (b) H. R. Warner and W. E. M. Lands, *J. Am. Chem. Soc.*, **85**, 60 (1963); (c) W. T. Norton, E. L. Gottfried, and M. M. Rapport, *J. Lipid Res.*, **3**, 456 (1962).

(14) G. V. Marinetti, J. Erbland, and E. Stotz, *J. Am. Chem. Soc.*, **80**, 1624 (1958).

tween the structures X and XI.[15] Compound X has been isolated[17] as a secondary product of the hydrolysis of natural plasmalogen.

In view of the simultaneous production of both 1- and 2-alkenylglycerols by the debromination of IV, an alternative route towards the synthesis of plasmalogens was devised and is described in a following paper.

Experimental[18]

(4-Dioxolanyl)methoxymethyl Triphenylphosphonium Iodide (VIII).—A mixture of 3.05 g. (0.02 mole) of 4-(chloromethoxymethyl)-1,3-dioxolane (VII)[8] and 5.25 g. (0.02 mole) of triphenylphosphine in 50 ml. of benzene was warmed to 50° for 15 min. and allowed to stand overnight at room temperature. The white crystalline hygroscopic phosphonium chloride (quantitative yield) was filtered and washed with benzene. It was dissolved in methanol and heated under reflux with sodium iodide for several hours until no further precipitate of sodium chloride formed. The solution was filtered, the filtrate was evaporated *in vacuo*, and the residue was crystallized from chloroform–ethyl acetate to give the phosphonium iodide, m.p. 179–180°.

Anal. Calcd. for $C_{23}H_{24}IO_3P$: C, 54.55; H, 4.78. Found: C, 54.51; H, 5.12.

(2,3-Dihydroxypropyl)oxymethyl Triphenylphosphonium Iodide (IX).—A solution of 2.35 g. of (4-dioxolanyl)methoxymethyl triphenylphosphonium chloride in 40 ml. of 0.1 *N* hydrochloric acid was heated to the boiling point in a stream of nitrogen. Boiling was continued until the distillate no longer gave a positive test for formaldehyde with aqueous 2,4-dinitrophenylhydrazine solution. Evaporation of the residue left the sirupy chloride (quantitative yield), which was heated under reflux with a solution of sodium iodide in methanol for 3 hr. Evaporation and crystallization of the residue from 2-propanol–ether gave the phosphonium iodide as prisms: m.p. 194–196°; infrared absorption, $\nu_{\max}$ 3322 cm.$^{-1}$ (—OH).

Anal. Calcd. for $C_{22}H_{24}IO_3P$: I, 25.65. Found: I, 25.52.

Hexadec-1-en-1-ol Acetate.—Prepared from *n*-hexadecanal, acetic anhydride, and anhydrous potassium acetate by the method of Bedoukian,[9] *n*-hexadec-1-en-1-ol acetate (39% yield) had b.p. 126–128° (0.1 mm.); $n^{24}\mathrm{D}$ 1.4491; infrared absorption, $\nu_{\max}$ 1760 (—OAc) and 1675 cm.$^{-1}$ (—O—C=C).

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 76.50; H, 12.13. Found: C, 75.97; H, 12.25.

2-Bromo-1,1-dimethoxyhexadecane.—Prepared from hexadec-1-en-1-ol acetate by the general method of Bedoukian,[9] 2-bromo-1,1-dimethoxyhexadecane was obtained as a waxy solid, m.p. 21–22°, b.p. 122° (0.01 mm.).

Anal. Calcd. for $C_{18}H_{37}BrO_2$: C, 59.14; H, 10.13. Found: C, 59.30; H, 9.67.

2-(*α*-Bromo-*n*-undecyl)-4-hydroxymethyl-1,3-dioxolane (IVa).—A mixture of glycerol (13.5 g.), 2-bromo-1,1-dimethoxydodecane[9] (25.4 g.), and sulfosalicylic acid (50 mg.) was heated gradually to 170° until the distillation of methanol had ceased. The mixture was cooled, treated with 5% sodium hydroxide solution and extracted with ether. Distillation of the dried ethereal extracts yielded 20.4 g. (75%) of the dioxolane, b.p. 140–150° (0.006 mm.), $n^{25}\mathrm{D}$ 1.4780.

Anal. Calcd. for $C_{15}H_{29}BrO_3$: C, 53.41; H, 8.67; Br, 23.69. Found: C, 53.45; H, 8.53; Br, 23.42.

2-(*α*-Bromo-*n*-pentadecyl)-4-hydroxymethyl-1,3-dioxolane (IVb).—Prepared in the same manner as IVa from *α*-bromohexadecanal dimethyl acetal, this dioxolane had b.p. 170–180° (0.01 mm.), $n^{24}\mathrm{D}$ 1.4779.

Anal. Calcd. for $C_{19}H_{37}BrO_3$: C, 58.76; H, 9.79. Found: C, 58.30; H, 9.39.

Preparation of the Mixture of 3-(1′-Dodecenyloxy)-1,2-propanediol (IIIa) and 2-(1′-Dodecenyloxy)-1,3-propanediol (Va).—A solution of 4.0 g. of 2-(*α*-bromo-*n*-undecyl)-4-hydroxymethyl-1,3-dioxolane in 100 ml. of 1,2-dimethoxyethane was treated with 1.0 g. of finely sliced lithium and the mixture was heated at 60° for 96 hr. Excess lithium was filtered off and water was cautiously added to the reaction mixture. The layers were separated and the aqueous phase was saturated with sodium chloride and extracted with ether. Distillation gave 2.75 g. (90% yield) of the mixture of glycerol *n*-dodecenyl ethers (IIIa and Va): b.p. 110–113° (0.02 mm.); $n^{25}\mathrm{D}$ 1.4642; infrared spectrum, $\nu_{\max}$ 3300, 1665, 927, and 734 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{30}O_3$: C, 69.70; H, 11.70. Found: C, 69.32; H, 11.54.

Preparation of the Mixed Glycerol *n*-Hexadecenyl Ethers (IIIb and Vb).—Application of the same method to 1.76 g. of 2-(*α*-bromo-*n*-pentadecyl)-4-hydroxymethyl-1,3-dioxolane gave 1.34 g. (95% yield) of the mixed glycerol *n*-hexadecenyl ethers (IIIb and Vb), b.p. 190–200° (0.014 mm.), as a waxy solid: m.p. 36–46°; $\nu_{\max}$ 3300, 1665, 927, and 734 cm.$^{-1}$. Its n.m.r. spectrum had the pattern shown in Figure 1 for the olefinic protons. Repeated distillation of this material gave a product, b.p. 165–166° (0.001 mm.), m.p. 45–47°, which showed no absorption at 1666 cm.$^{-1}$, and no olefinic protons in its n.m.r. spectrum.

Anal. Calcd. for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.80; H, 12.12.

Reaction with Brady's reagent gave, after a few minutes' warming, palmitaldehyde 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 104–106°.

Acetylation of the Mixture of Dodecenyl Glycerol Ethers.—The mixture (1.10 g.) of dodecenyl glycerol ethers (IIIa and Va) obtained above was dissolved in 5 ml. of dry pyridine, 2.5 ml. of acetic anhydride was added, and the mixture was allowed to stand at room temperature for 24 hr. The solvent was then removed on a rotary evaporator and the product was distilled through a short tube (air-bath temperature 195–200° at 0.01 mm.) to give 1.14 g. of a liquid: $n^{21}\mathrm{D}$ 1.4506; $\nu_{\max}$ 1745, 1664, 927, and 738 cm.$^{-1}$. Vapor phase chromatography was carried out using a 10-ft. column packed with 30% QF-1 fluorosilicone on Celite. The carrier gas was helium (at 15 p.s.i.) and the column temperature 220°. The product was shown to be a mixture of two components, A (retention time 26 min.) and B (retention time 33 min.), in the ratio of 4:5. Preparative vapor phase chromatography was carried out using the same conditions with repeated injections of 0.1 ml. of the mixture. Components A and B had the following properties.

Component A, $n^{18}\mathrm{D}$ 1.4510, consisted of a mixture of *cis*-III and *cis*-V, and its n.m.r. spectrum showed a multiplet at δ = 5.96 p.p.m., with J = 6.5 c.p.s.; the infrared spectrum showed $\nu_{\max}$ 1745, 1664, 1114, 1052, and 734 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.03; H, 10.09.

Component B, $n^{18}\mathrm{D}$ 1.4527, consisted of a mixture of *trans*-III and *trans*-V, and its n.m.r. spectrum had a multiplet at δ = 6.25 p.p.m., with J = 12.5 c.p.s.; the infrared spectrum showed $\nu_{\max}$ 1745, 1660–1670, 1167, 1052, and 927 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.80; H, 10.11.

Preparation of Mixed *n*-Dodecyl Glycerol Ethers.—The method used for components A and B was the same. A solution of 25 mg. of the pure component (obtained from v.p.c.) in ethyl acetate was hydrogenated in the presence of 20 mg. of Adams catalyst in a Parr apparatus at 40 p.s.i. of hydrogen for 3.4 hr. Filtration and removal of catalyst left a residue which no longer showed infrared absorption in the 6.0-μ region. The residue was dissolved in 1.5 ml. of methanol and treated with 0.2 ml. of 10% sodium hydroxide solution at room temperature for 16 hr. The mixture was poured into water and extracted with ether, the dried extracts were evaporated, and the residue was dissolved in ethanol and filtered through Celite. Removal of the solvent *in vacuo* gave a solid product which was free from acetate absorption in its infrared spectrum. This material was used for the periodate oxidation.

Determination of 1,2-Glycol.—The method employed was that of Marinetti, *et al.*,[14] in which the consumption of periodate is

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[15] A referee kindly pointed out that a paper[16] which appeared after this manuscript was submitted gives the dioxolane structure X for these compounds.

[16] C. Piantadosi, M. F. Frosolono, C. E. Anderson, and A. F. Hirsch, *J. Pharm. Sci.*, **53**, 1024 (1964).

[17] (a) J. B. Davenport and R. M. C. Dawson, *Biochem. J.*, **79**, 10P (1961); (b) R. Pietruszko and G. M. Gray, *Biochim. Biophys. Acta*, **56**, 232 (1962).

[18] Melting points were determined using a Kofler hot stage or a Thomas–Hoover electric melting point apparatus and are corrected. Infrared spectra were measured on a Beckman IR-5 instrument. N.m.r. spectra were obtained on a Varian A-60 spectrometer in deuteriochloroform solution and chemical shifts are reported in p.p.m. (δ) measured downfield from tetramethylsilane used as an internal reference. Analyses were carried out by the Microanalytical Laboratory, University of California, Berkeley, Calif.

followed spectrophotometrically by the change of optical density at 300 mμ. Chimyl alcohol was used as a standard, as follows. A solution of 1.84 mg. of chimyl alcohol in 4 ml. of 95% ethanol was treated with 0.1 ml. of a 0.2 *M* phosphate buffer solution (pH 7.4), and to this mixture was added 1.0 ml. of a 0.01 *M* sodium periodate solution. The change of optical density with time was recorded; the optical density at the start of the reaction was obtained by extrapolation.[19] One molar equivalent of periodate was consumed in 5 hr, which was taken as the standard time required for complete reaction under these conditions. In separate duplicated runs, the *n*-dodecyl glycerol ethers obtained respectively from components A and B each contained 0.47 ± 0.03 mole of 1,2-glycol/mole of substance.

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[19] G. V. Marinetti and G. Rouser, *J. Am. Chem. Soc.*, **77**, 5345 (1955).

Reaction of Pyridine and Quinoline N-Oxides with Phenylmagnesium Bromide

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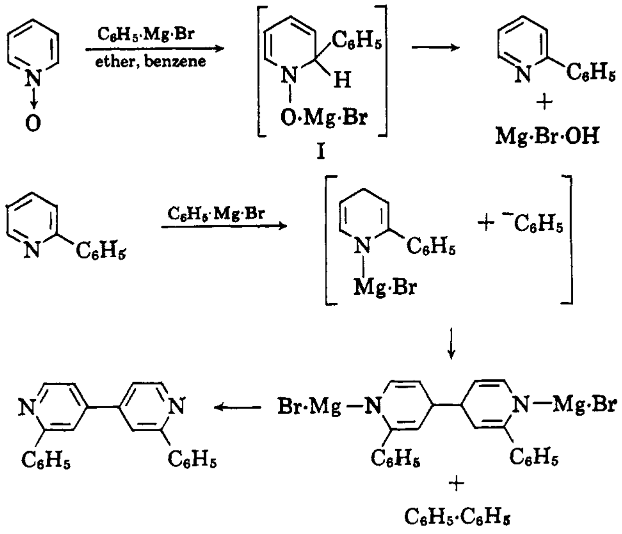
Reactions of pyridine and quinoline N-oxides with phenylmagnesium bromide in tetrahydrofuran are described. Pyridine N-oxide is converted to 1-hydroxy-2-phenyl-1,2-dihydropyridine (III) in 60–80% yield. III is easily dehydrated to give 2-phenylpyridine. Quinoline N-oxides (X) are converted to 2-phenylquinoline N-oxide derivatives (XI) as main products with 2-phenylquinolines (XII) as by-products. If the reaction is carried out at lower temperature 1-hydroxy-2-phenyl-1,2-dihydroquinoline (VII) is obtained.

There is considerable literature dealing with the Grignard reaction of pyridine and quinoline compounds,[1-9] but only a few references are available concerning the Grignard reaction with their N-oxides. In 1936, Colonna[10] reported the reaction of pyridine N-oxide and quinoline N-oxide with phenylmagnesium bromide in ether to give 2-phenylpyridine and 2-phenylquinoline, respectively. Ochiai[11] re-examined this reaction in benzene as a solvent, and described the reaction as shown in Scheme I with 2-phenylpyridine (13%), 2,2′-diphenyl-4,4′-bipyridine (4%) and biphenyl as the products. However, neither of the dihydro derivatives (I or II) was isolated as stable intermediates.

During the course of an investigation on the synthesis and reactions of phenylpyridine derivatives, attention in our laboratory was focused upon the Grignard reaction mentioned above. Because of poor yields, the Grignard reaction has not been a practical method of synthesis. Therefore, it was thought advisable to find improved conditions or another route of synthesis for 2-phenylpyridine. On the other hand, tetrahydrofuran (THF) is known to an excellent solvent for the Grignard reaction.[12] This paper describes the reaction of pyridine and quinoline N-oxides with phenylmagnesium bromide in THF as a solvent in place of ether or benzene to give dihydro intermediates as stable compounds in good yields. This method is practical for the synthesis of 2-phenylpyridine and 2-phenylquinoline derivatives.

SCHEME I[11]



Reaction of Pyridine N-Oxide with Phenylmagnesium Bromide.—When pyridine 1-oxide was allowed to react with phenylmagnesium bromide in THF, white needles of a compound, $C_{11}H_{11}ON$ (III), were obtained as the main product (60–80%) with 2-phenylpyridine and 2,2′-diphenyl-4,4′-bipyridine as by-products. Compound III was soluble in 10% sodium hydroxide and in organic solvents except for petroleum ether, but it was insoluble in 10% sodium carbonate and 10% hydrochloric acid. The ferric chloride color test for phenolic compounds was negative. A dry distillation with zinc dust or heating of III to 200° gave 2-phenylpyridine and water. Upon treatment with acetic anhydride, III was converted to 2-phenylpyridine. The oxidation of III with potassium permanganate in sodium hydroxide solution gave benzoic acid (see Scheme II).

The n.m.r. spectrum of III shows a doublet at τ 1.5 (J = 10 c.p.s., one proton at the 2-position of the pyridine ring), a complex multiplet at 2.51–2.73 (five protons of benzene), a complex multiplet at 2.98–4.05 (four vinyl protons of the pyridine ring), and one proton at 0.8 (=N—OH). The presence of methylene protons was not observed. These data are consistent with the 1,2-dihydropyridine structure III, but not with the isomeric 1,4-dihydro compound III′.

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