distinguishable from that of *d*-3-hydroxy-N-methylisomorphinan prepared by hydrogenation of the corresponding *d*-Δ^6-dehydro compound (*vide supra*).

Anal. Calcd. for $C_{17}H_{25}ON$: C, 79.33; H, 9.01. Found: C, 79.43; H, 9.51.

Its methiodide, prepared in ethyl acetate and crystallized from alcohol, melted at 255–258° dec.

Anal. Calcd. for $C_{18}H_{28}ONI$: C, 54.14; H, 6.56. Found: C, 54.42; H, 6.77.

Its hydriodide, crystallized from water, melted at 154–156°, colorless plates.

Anal. Calcd. for $C_{17}H_{24}ONI \cdot {}^1/_2H_2O$: C, 51.78; H, 6.39. Found: C, 51.49, 52.02; H, 6.35, 6.50.

***l*-3-Hydroxy-N-methylisomorphinan** was recovered in like manner from its dibenzoyl-D(−)-tartrate (4.74 g.). After recrystallization from benzene–cyclohexane, 1.95 g. of colorless fine felty needles, m.p. *ca.* 110°, solidification, remelting at 171–173°, $\alpha^{25}D$ −53.8°, was obtained.

Anal. Calcd. for $C_{17}H_{25}ON$: C, 79.33; H, 9.01. Found: C, 79.80; H, 9.33.

Its methiodide, prepared and crystallized as above, melted at 255–257.5° dec.

Anal. Calcd. for $C_{18}H_{28}ONI$: C, 54.14; H, 6.56. Found: C, 54.32; H, 6.75.

Its hydriodide, crystallized from water, melted at 153–156°, colorless plates.

Anal. Calcd. for $C_{17}H_{24}NI \cdot {}^1/_2H_2O$: C, 51.78; H, 6.39. Found: C, 52.10, 52.01; H, 6.45, 6.39.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

The Total Synthesis of Sphingosine[1]

BY D. SHAPIRO, H. SEGAL AND H. M. FLOWERS

RECEIVED OCTOBER 2, 1957

The synthesis of DL-1,3-dihydroxy-2-amino-4-octadecene (VIII) and its optical resolution is described. The key intermediate, ethyl 2,3-dioxo-4-octadecenoate-2-phenylhydrazone (III) is reductively acetylated to the amide IV. Selective reduction with sodium borohydride, followed by hydrolysis of the carbinol VI leads to the ester hydrochloride VII which is reduced to racemic sphingosine.

Sphingosine was discovered in 1882 by Thudichum who obtained it as a waxy unstable substance from hydrolysis of a lipid fraction of brain tissue. Early investigators[2–4] recognized it as dihydroxyaminoöctadecene. However, no convincing evidence for the relative position of the three functional groups was presented until 1947, when Carter and co-workers[5–6] established the correct structure of sphingosine. The D-configuration of the carbons 2 and 3 was confirmed by several investigators.[7–11] More recently, it has been shown by Mislow,[12] and Marinetti and Stotz,[13] that the double bond has the *trans* form. Taken together, these results have conclusively established the structure of sphingosine as *trans*-D-*erythro*-1,3-dihydroxy-2-amino-4-octadecene (VIII). In a recent communication[14] we announced the synthesis of the racemic base. More recently, a synthesis of sphingosine and its isomers has been described by Grob and Gadient.[21] In this paper we wish to report the total synthesis of sphingosine.

A Knoevenagel–Doebner condensation of myristaldehyde with malonic acid gave a fairly good yield of *trans*-2-hexadecenoic acid. We found this new approach to the hexadecenoic acid more satisfactory than the method of Ponzio[15] which involves dehydroiodination of α-iodopalmitic acid and gives poor yields after repeated crystallization. Ethyl 2-acetyl-3-oxo-4-octadecenoate (I) was obtained in a 75% yield by treatment of pure hexadecenoyl chloride with ethyl sodioacetoacetate. It was found, however, that slightly decomposed acid chloride gave predominantly the O-acyl isomer IX.[16]

In the past 15–20 years the Japp–Klingemann reaction[17a] has been applied to the synthesis of various amino acids. This method, which was developed by Feofilaktov,[17b] is based on the coupling of a diazonium salt with alkyl substituted acetoacetic esters. However, the formation of a phenylhydrazone of the type described in this paper is, apparently, the first example of a Japp–Klingemann reaction carried out on an α,α-diacyl ester in which one of the acyl groups is α,β-unsaturated. Thus Bülow,[18] in 1902, reported the failure to couple a diazonium salt with ethyl cinnamoylacetoacetate. After an intensive study we found that reactions of this type can be realized under a number of carefully controlled conditions, and we were able to obtain not only the phenylhydrazone

(1) Presented in part before the XIVth International Congress of Pure and Applied Chemistry, Zürich, 1955.

(2) P. A. Levene and C. J. West, *J. Biol. Chem.*, **16**, 549 (1913).

(3) P. A. Levene and C. J. West, *ibid.*, **18**, 481 (1914).

(4) E. Klenk, *Z. physiol. Chem.*, **185**, 169 (1929).

(5) H. E. Carter, F. J. Glick, W. P. Norris and G. E. Phillips, *J. Biol. Chem.*, **170**, 285 (1947).

(6) H. E. Carter, F. J. Glick, W. P. Norris and G. E. Phillips, *ibid.*, **142**, 449 (1942).

(7) H. E. Carter and C. G. Humiston, *ibid.*, **191**, 727 (1951).

(8) J. Kiss, G. Fodor and D. Banfii, *Helv. Chim. Acta*, **37**, 1471 (1954).

(9) E. Klenk and H. Faillard, *Z. physiol. Chem.*, **299**, 48 (1955).

(10) H. E. Carter, D. Shapiro and J. B. Harrison, THIS JOURNAL, **75**, 1007 (1953).

(11) H. E. Carter and D. Shapiro, *ibid.*, **75**, 5131 (1953).

(12) K. Mislow, *ibid.*, **74**, 5155 (1952).

(13) G. Marinetti and E. Stotz, *ibid.*, **76**, 1347 (1954).

(14) D. Shapiro and K. H. Segal, *ibid.*, **76**, 5894 (1954).

(15) G. Ponzio, *Chem. Zentr.*, **76**, **I**, 804 (1905).

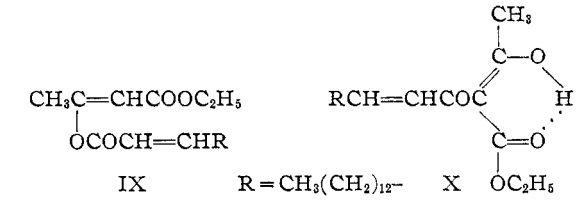
(16) (a) The C-acyl structure of (I) is supported by the absence of an absorption at about 1750–1755 cm.$^{-1}$ which would be expected of IX as an α,β-unsaturated vinyl ester (L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 155–156); (b) as the infrared spectrum of I shows no ester band, it may be formulated as X where the ester carbonyl group, chelated to the enolic hydroxyl, is characterized by a band at 1644 cm.$^{-1}$.

(17) (a) F. R. Japp and F. Klingemann, *Ber.*, **20**, 2942, 3284, 3398 (1887); (b) V. V. Feofilaktov, *Compt. rend. (Doklady) acad. sci. U.R.S.S.*, **24**, 755 (1939).

(18) C. Bülow and E. Hailer, *Ber.*, **35**, 933 (1902).

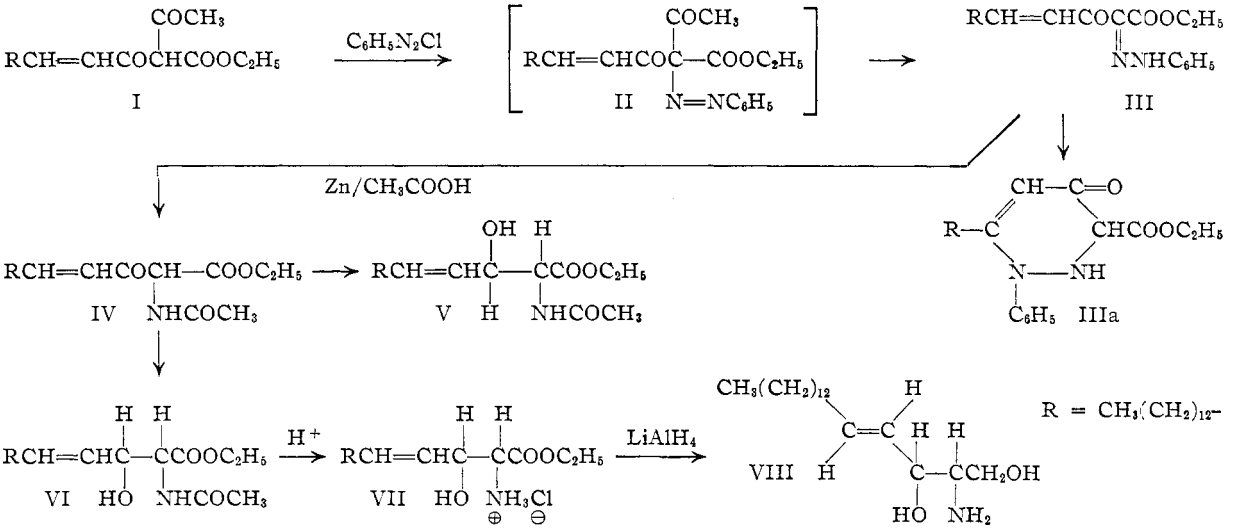
III but also the corresponding cinnamoyl derivative (III, R = C_6H_5–) in yields up to 80%.

In the course of our study we made the surprising observation that the presence of ammonium salts, such as ammonium chloride or acetate, promotes the Japp–Klingemann reaction. That this is not merely a salting-out effect was shown by a



IX R = $CH_3(CH_2)_{12}$– X

REACTION SCHEME



number of experiments in which these salts were omitted; in no such case could any product be isolated. It is possible that the ammonium ion facilitates the deacetylation of the intermediate II prior to its transformation to the phenylhydrazone III. A similar deacylating effect of the ammonium ion is reported in the literature.[19]

Occasionally, the Japp–Klingemann reaction took an abnormal course and, as a result, a higher melting isomeric substance was obtained in good yield as the sole reaction product. In the hope of finding the conditions under which the formation of this undesirable substance could be avoided, we studied the nature of this isomerization more closely.[20] The unknown isomer was soon recognized as the pyridazinone derivative IIIa which most probably was formed by cyclization of III *via* an internal Michael-type reaction, followed by migration of the C=N double bond.

Reduction of the dry phenylhydrazone to the acetamido ester IV proceeded satisfactorily, when the time of reaction was limited to 1.5–2 hours. After prolonged treatment with zinc and acetic acid two by-products were isolated (m.p. 85–86° and 92–94°) which, although formed in small amounts, made the purification of the main reaction product difficult.

(19) R. L. Shriner and A. G. Schmidt, THIS JOURNAL, **51**, 3636 (1929).

(20) D. Shapiro, R. A. Abramovitch and S. Pinchas, *ibid.*, **78**, 2144 (1956).

Selective reduction of IV with sodium borohydride gave rise to the formation of both diastereomeric alcohols V and VI in an approximate ratio of 2:3. Since natural sphingosine has the *erythro* configuration, we directed our main attention toward the investigation of the *erythro* isomer VI.[22] For deacetylation, the pure carbinol VI was treated with a warm mixture of diluted hydrochloric acid and dioxane, and the ester hydrochloride VII was obtained in 45–50% yield. This comparatively low yield is probably to be ascribed to a partial inversion to the *threo* isomer. Such an isomerization was first observed by Welsh[22] who found that ephedrin (*erythro*) is inverted to the more stable ψ-

Fig. 1.—Top, infrared spectrum of DL-sphingosine (in chloroform): main bands 3375, 2915, 2850, 1586, 1467, 1374, 1086, 1023, 975 cm.$^{-1}$. Bottom, infrared spectrum of synthetic D-triacetylsphingosine (in chloroform): main bands 3440, 2920, 2860, 1730, 1675, 1510, 1467, 1373, 1255, 1047, 974 cm.$^{-1}$.

ephedrin (*threo*) under similar conditions. This explains the poor yields of VII which resulted from direct hydrolysis of the original mixture of the two diastereomers V and VI.

(21) C. A. Grob and F. Gadient, *Helv. Chim. Acta*, **40**, 1145 (1957). The authors describe the *threo* isomer which they obtained as a waxy substance.

(22) L. H. Welsh, THIS JOURNAL, **71**, 3500 (1949).

Finally, the ester hydrochloride VII was reduced with an excess of lithium aluminum hydride, and racemic sphingosine was obtained in a 50–60% yield. After 2–3 crystallizations, the base of m.p. 71–73° was pure enough for the optical resolution.

Various attempts to purify the base through its triacetyl derivative failed. We found that acid hydrolysis caused considerable destruction of the molecule. This result is in agreement with the reported instability of various natural derivatives of sphingosine toward acid hydrolyses.

Experimental

Infrared measurements were carried out using a Perkin-Elmer model 12C spectrophotometer equipped with a rock-salt prism.

trans-**2-Hexadecenoic Acid.**—Forty-three grams of myristaldehyde was added to a solution of 24 g. of malonic acid in 50 cc. of pyridine at a temperature not exceeding 35°. After addition of 1.5 cc. of piperidine the mixture was warmed for one hour at 50–55° and for 3 hours at 80–90°. The reaction product was poured into ice-water, 50 cc. of concentrated hydrochloric acid was added and the mixture was extracted with ether. The oily residue was taken up with 75 cc. of petroleum ether (60–80°) and cooled overnight; yield 35 g., m.p. 48–49°.

trans-**2-Hexadecenoyl Chloride.**—To a warm solution of 57 g. of hexadecenoic acid in 90 cc. of dry petroleum ether, was added with stirring, over a period of 15 minutes, 40 cc. of thionyl chloride (purified by distillation over bees wax). Refluxing was continued for 4 hours. After distilling off the solvent and the excess of thionyl chloride *in vacuo*, the latter was removed as completely as possible by distilling the residue twice with 50-cc. portions of petroleum ether; b.p. 145–148° (0.05 mm.), yield 55 g.[23] The chloride distilled at 145–148° (0.05 mm.) as a slightly yellow liquid, $n^{25}D$ 1.4644.

Anal. Calcd. for $C_{16}H_{29}ClO$: C, 70.46; H, 10.7; Cl, 13.2. Found: C, 70.40; H, 11.0; Cl, 12.9.

Ethyl 2-Acetyl-3-oxo-4-octadecenoate (I).—To a suspension of 8.46 g. of powdered sodium in 1250 cc. of ether was added 56 g. of ethyl acetoacetate and the mixture was stirred for about 4 hours at room temperature, until all sodium had reacted. The suspension was then cooled to 5° and 94 g. of pure hexadecenoyl chloride was added with stirring during 2–3 minutes. Stirring was continued at room temperature for 16–18 hours. The slightly turbid solution was then poured into water and enough ice to maintain the temperature at about +5°, and 125 cc. of 20% sulfuric acid was added. The ether layer was washed to neutral, dried and evaporated. The remaining oil was taken up with two volumes of ethanol, cooled while scratching with a rod until crystallization set in, and left overnight in the refrigerator. The ester was filtered, washed with a little cold ethanol and recrystallized from 800 cc. of ethanol; yield 80 g., m.p. 34–35.5°; infrared spectrum: 2935, 2860, 1701, 1644, 1560, 1414, 1340, 1138, 975 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{38}O_4$: C, 72.1; H, 10.4. Found: C, 72.2; H, 10.6.

Ethyl 2,3-Dioxo-4-octadecenoate-2-Phenylhydrazone (III).—A standard diazo solution was prepared from 28 g. of aniline, 100 cc. of hydrochloric acid (sp. gr. 1.19), 330 cc. of water and a solution of 21.5 g. of sodium nitrite in 40 cc. of water. This solution amounted to 500 cc. and was partly neutralized with 36 g. of sodium carbonate (dissolved in 360 cc. of water) at −5°, before use.

A solution of 14.4 g. of the ester I in one liter ethanol was cooled to 12°, then 32 cc. of sodium acetate solution (45 g. of sodium acetate in 50 cc. of water) and 20 g. of ammonium chloride were added, followed immediately by 120 cc. of the neutralized diazo solution. The latter was added during 2–3 minutes with vigorous stirring. After 30 minutes, 100 cc. of ether was added in a thin stream. A flocculent yellow precipitate was soon formed, and vigorous stirring was continued for one hour at 8–10°. After cooling overnight in a refrigerator, the product was filtered, washed with cold 70% ethanol, then with cold water and dried *in vacuo* over calcium chloride; yield 14–15 g., m.p. 37–39°. The phenylhydrazone thus prepared, in most cases, was pure enough for the next reaction. It can be crystallized from petroleum ether.[24] The product is not stable and should be kept in the cold; infrared spectrum: 2945, 2880, 1708, 1645, 1580, 1511, 1459, 1396, 1377, 1267, 1200, 1138, 1118, 1088 and 983 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}N_2O_3$: C, 72.8; H, 9.3; N, 6.5; OEt, 10.5. Found: C, 72.9; H, 9.5; N, 6.2; OEt, 9.7.

Ethyl 2-Acetamido-3-oxo-4-octadecenoate (IV).—A solution of 11.25 g. of the phenylhydrazone in 100 cc. of glacial acetic acid was added dropwise, with good stirring, over a period of 75–90 minutes to a suspension of 15 g. of zinc powder in 60 cc. of glacial acetic acid and 25 cc. of acetic anhydride, the temperature being maintained at 20–22°. After the addition, stirring was continued until the yellow color of the solution had completely disappeared. The zinc was filtered off, washed with glacial acetic acid and the filtrate poured into ice-water. The oily precipitate solidified after shaking for a few minutes. The product was collected, washed with cold water and dried over calcium chloride; yield 9.3 g. After recrystallization from methanol, it melted at 63–65°.

Anal. Calcd. for $C_{22}H_{39}NO_4$: C, 69.3; H, 10.2; N, 3.6. Found: C, 69.8; H, 10.6; N, 4.0.

Ethyl *erythro*-2-Acetamido-3-hydroxy-4-octadecenoate (VI).—A solution of 10 g. of the acetamido ester in 400 cc. of methanol was treated at 10–15° with a solution of 0.5 g. of sodium borohydride in 10 cc. of water to which 4 drops of *N* sodium hydroxide solution had been added. The solution was kept at this temperature for 30 minutes, poured into a mixture of 300 cc. of ice-water and 300 cc. of saturated sodium chloride solution, and extracted twice with ether. After washing several times with water to remove the methanol, the ether was dried and evaporated *in vacuo*. The oily residue was recrystallized twice or thrice from 8–10 volumes of petroleum ether (60–80°), the first time in the cold, then preferably at 27–30°; yield of the *erythro* isomer 4.8 g., m.p. 64–67°.

Anal. Calcd. for $C_{22}H_{41}NO_4$: C, 68.9; H, 10.7; N, 3.6. Found: C, 68.9; H, 10.8; N, 3.6.

Ethyl *erythro*-2-Amino-3-hydroxy-4-octadecenoate Hydrochloride (VII).—The above carbinol (3.6 g.), was refluxed for 2 hours with 30 cc. of 5% hydrochloric acid and 30 cc. of dioxane. To the cooled solution 30 cc. of 6 *N* hydrochloric acid was added and the mixture was allowed to stand for several hours in the refrigerator. The precipitate was extracted, while cold, twice with ether, and the solution was cooled overnight. The precipitated ester hydrochloride was filtered quickly and dried *in vacuo*, first over sulfuric acid, then over phosphorus pentoxide. The filtrate may be concentrated to give more product, though of poorer quality. The dry product, 1.5–1.8 g., was crystallized from dioxane and a little tetrahydrofuran, or from ethyl acetate, and the crystals were washed with dry ether; m.p. 110–112°.

Anal. Calcd. for $C_{20}H_{40}NO_3Cl$: C, 63.4; H, 10.7; N, 3.7; Cl, 9.4. Found: C, 63.5; H, 10.8; N, 4.0; Cl, 9.6.

trans-DL-*erythro*-**1,3-Dihydroxy-2-amino-4-octadecene (VIII).**—A solution of 0.7 g. of the ester hydrochloride in 35 cc. of dry tetrahydrofuran was added, with stirring over a period of 20 minutes, to a suspension of 2 g. of lithium aluminum hydride in 50 cc. of ether. After the addition was complete the mixture was gently refluxed for 1.5 hours. Decomposition with water at 0° was followed by addition of 10% sodium hydroxide solution and extraction with ether. The oily residue, crystallized from ethyl acetate, or from ether and a little petroleum ether, gave 0.35 g. of the fairly pure base, melting at 71–73°.

Anal. Calcd. for $C_{18}H_{37}O_2N$: C, 72.2; H, 12.4; N, 4.7. Found: C, 72.3; H, 12.3; N, 5.1.

The triacetyl derivative, prepared from the base and acetic anhydride in the presence of pyridine, was recrystallized from petroleum ether and melted at 90–91°.

Anal. Calcd. for $C_{24}H_{43}NO_5$: C, 67.7; H, 10.1; N, 3.3. Found: C, 67.9; H, 10.3; N, 3.6.

trans-D-*erythro*-**1,3-Dihydroxy-2-amino-4-octadecene.**—A solution of 0.5 g. of DL-sphingosine in 15 cc. of ethanol was

(23) For reasons indicated in the text, it is necessary to repeat the distillation once or twice.

(24) Crystallization from ethyl alcohol converted the product into the isomeric pyridazinone IIIa.

added to a warm solution of 0.250 g. of D-glutamic acid[25] in 30 cc. of 50% ethanol. After evaporation to dryness, the salt was dissolved in 80 cc. of diluted alcohol (100 cc. of alcohol + 10 cc. of water) and left overnight at 22°. After three crystallizations from diluted alcohol, the glutamate had a constant m.p. of 136–138°. The salt was dissolved in warm water and a little ethanol, the solution was made alkaline with *N* sodium hydroxide and extracted with ether. After evaporation of the ether, the base was converted into the triacetyl derivative which was recrystallized from acetone and melted sharply at 103.5–104°, $[\alpha]^{24}D$ −12.8°. The natural triacetyl derivative[26] has $[\alpha]^{25}D$ −11.7° and m.p. 101–102°.

(25) Glutamic acid was first used by Grob for the resolution of dihydrosphingosine; C. A. Grob and E. F. Jenny, *Helv. Chim. Acta*, **35**, 2106 (1952).

(26) H. E. Carter, W. P. Norris, F. J. Glick, G. E. Phillips and R. Harris, *J. Biol. Chem.*, **170**, 269 (1947).

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

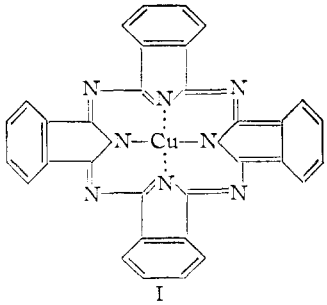
Polymeric Phthalocyanines[1]

BY C. S. MARVEL AND JOHN H. RASSWEILER

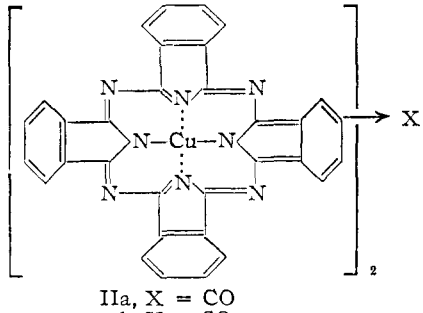
RECEIVED SEPTEMBER 23, 1957

Low molecular weight soluble polymeric phthalocyanines have been prepared from mixtures of pyromellitic acid and phthalic anhydride and of 3,3′,4,4′-tetracarboxydiphenyl ether and phthalic anhydride. The polymers are dark blue-green to black powders with fair heat stability and which show visible absorption bands and infrared absorption bands characteristic of phthalocyanines.

Copper phthalocyanine (I) has been found to have great thermal stability since it can be sublimed under nitrogen at 560° without decomposition.[2] The work described in this communication was undertaken to see whether this unit might be incorporated into a polymeric structure to produce an equally thermostable polymer.



I



IIa, X = CO
b, X = SO_2

Dyes containing two phthalocyanine residues (IIa and b) have been prepared by use of a ratio of six parts phthalonitrile to one part of 3,3′,4,4′-tetracyanobenzophenone and of the same ratios of phthalonitrile and 4-cyanodiphenylsulfone-3,3′,4′-tricarboxylic acid.[3] This proves that mixed units can be introduced into a phthalocyanine structure and hence by use of properly substituted aromatic molecules it should be possible to arrive at polymeric phthalocyanines. In fact, workers at the Sprague Electric Co.[4] have prepared some polymeric phthalocyanines from 3,3′,4,4′-tetracyanobiphenyl, and Bailar and Drinkard[5] have prepared polymers from pyromellitic acid and urea under phthalocyanine-forming conditions. However, in both of these cases the polymeric products are quite insoluble and the characterizations of the polymers were difficult.

We have used the principle of introducing mixed aromatic systems into the phthalocyanine-forming reaction to produce linear polymers which are soluble and more readily studied. Two systems have been used with some success. These are pyromellitic acid, phthalic anhydride and urea, and 3,3′,4,4′-tetracarboxydiphenyl ether, phthalic anhydride and urea. It was hoped that the first would give a polymer with the recurring unit shown in formula III or the second would yield copolymers with the recurring unit shown in formula IV. It is, of course, realized that the individual units in the phthalocyanine structure may not be so symmetrically arranged as this idealized case but the over-all structure might be that of a linear polymer if the tetrasubstituted and disubstituted aromatic units could be introduced into the molecule in equal molar quantities.

The 3,3′,4,4′-tetracarboxydiphenyl ether was prepared from 3,4-dimethylphenol and 4-bromo-1,2-dimethylbenzene by making first the aryl ether and then oxidizing with potassium permanganate.

When a ratio of three moles of phthalic anhydride to one mole of either of the above tetrasubstituted aryl acids was heated under phthalocyanine-form-

(1) The work discussed herein was initiated as part of the synthetic rubber research project sponsored by the National Science Foundation and completed under contract number AF-33(616)-3772 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio; Lt. L. E. Coleman, project engineer.

(2) R. P. Linstead, *J. Chem. Soc.*, 1027 (1934).

(3) A. Bucher, U. S. Patent 2,492,732 (December 27, 1949).

(4) Sprague Electric Co. Final Report under contract No. D.A.-36-039-SC-87 to the United States Signal Corps, May 14 through October 15, 1952; ASTIA AD No. 6116.

(5) W. C. Drinkard, Ph.D. Thesis under Professor J. C. Bailar, University of Illinois, 1956.