Summary

The ortho, meta and para isomers of ethylbiphenyl, acetylbiphenyl, biphenylmethylcarbinol and vinylbiphenyl have been synthesized and characterized. *p*-Ethylbiphenyl has been shown to melt at 34° instead of 47° as previously reported. An improved synthesis of *m*-bromobiphenyl is described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Further Studies on Steric Deformation[1]

BY RUDOLPH C. ELLINGSON[2] AND ALSOPH H. CORWIN

In the preceding paper of this series McEwen[1] has recorded the preparation of N-methyl etioporphyrin I and some of its derivatives. This substance, as was pointed out, is unusual in the degree of crowding of its atoms. Because of their theoretical importance, we have examined McEwen's synthetic method and structural conclusions in greater detail. Our conclusion, reached by methods described below, is that the structure assigned to N-methyletioporphyrin I is correct and that explanations of the peculiar chemistry of this and related substances must proceed from this premise.

The work reported in this paper was performed upon N-methyletioporphyrin II because of the readier availability of this than of N-methyletioporphyrin I. In addition to confirming the position of the added methyl group on a nitrogen in the porphyrin, we have discovered two reactions which cleave the methyl group from the ring. These strengthen the hypothesis that the methylated porphyrin is highly strained and demonstrate that this strain manifests itself in decreased chemical stability of the molecule. This is a clear-cut geometrical or stereochemical effect on reactivity. Much of the energy necessary to break the ordinarily stable C–N bond is supplied in this instance by relieving the steric deformation due to the crowded position of the methyl group in the center of the molecule.

With respect to preparation, our studies confirmed McEwen's report that dimethyl sulfate does not methylate the alkali salts of the porphyrin. His method of heating the porphyrin with alkyl iodides proved the most satisfactory. Use of the di-sodium salt of the porphyrin was found, however, to hinder rather than to help the reaction. Products of high purity were obtained by chromatographic adsorption.

To secure greater analytical differentiation, an attempt was made to prepare higher N-alkyl porphyrins. Mono-N-ethyletioporphyrin II was prepared successfully but in much lower yield. The *n*-propyl and *n*-butyl derivatives could not be prepared by the iodide method.

The constitutional problem was attacked from several angles. Carbon and hydrogen analyses for both the N-methyl and N-ethyl derivatives proved to be consistent with the postulated structures. The active hydrogen determination with methylmagnesium iodide showed the presence of only one active hydrogen instead of two as in the parent porphyrin. Compelling evidence for the acceptance of the postulated formula was finally obtained, however, by oxidative degradation of the N-methylporphyrin. The oily N-methylethyl-methylmaleic imide obtained was hydrolyzed and the methylamine formed was identified. This establishes the presence of a CH_3-N linkage in the porphyrin and, combined with the other evidence adduced, establishes the constitution of these alkylated porphyrins as N-alkyl porphyrins. New N-alkyl etio-porphyrins can be identified readily by the characteristic shift in the absorption spectrum. This resembles qualitatively the shift produced by the introduction of methyl groups into dipyrrylmethenes. The addition of two methyls to a symmetrical methene shifted the absorption maximum toward longer wave lengths by 400 Å., whereas the addition of a single methyl group in the porphyrin shifted each of the absorption bands to longer wave lengths by smaller amounts. The shifts in the four strong bands of the porphyrin, reading from the violet to the red, were +80, +50, +190, and +200 Å.

It is possible to imagine two models of an N-methyl porphyrin, one in which the methyl group is coplanar with the porphyrin ring, the other in which the CH_3-N bond is bent so that the methyl group is out of the plane of the ring. Sufficient data to permit a decision between these possibilities are not now at hand. Robertson[3] has shown that the phthalocyanine nucleus is capable of undergoing considerable deformation to accommodate smaller and larger metals in the center of the ring. Figure 1 is a model of an N-methylporphyrin using bond angles found in Robertson's studies. The large ring has been compressed from the sides and the pyrrole rings have been compressed from the center to increase the distance between two opposite nitrogens and permit maximum accommodation of the methyl group within the lim-

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(1) Studies in the Pyrrole Series. XVI; Paper XV, McEwen, THIS JOURNAL, **68**, 711 (1946).

(2) Present address, Research Laboratory, Mead Johnson and Company, Evansville, Indiana.

(3) Robertson, *J. Chem. Soc.*, 1204 (1936); Robertson and Woodward, *ibid.*, 221 (1937); 40 (1940).

its imposed by the X-ray observations. The small continuous circles are van der Waals radii of hydrogen (1.2 Å.), the large circle is the corresponding radius of CH_3 (2.0 Å.) and the broken circles are the radii of the ring nitrogens (1.5 Å.).

It will be seen from this model that accommodation of the methyl group with the opposite hydrogen can be achieved more readily than with the adjacent nitrogens. Some further bond bending and interpenetration of van der Waals radii might permit the molecule actually to assume the coplanar structure. It might be argued that the non-coplanar structure appears more reasonable, however. Certainly in the case of the cupric chloride complex of N-methyletioporphyrin I, characterized by McEwen,[1] this must be the explanation of the existence of the compound, since the possibility of interpenetration of methyl and copper seems much less likely than that of methyl and hydrogen.

The fact that energy is expended somehow in the accommodation of the methyl group to the porphyrin nucleus is illustrated by the ease with which cleavage can be brought about. N-Methyletioporphyrin II melts at 205–210° with decomposition. At this temperature, all the methylated compound is destroyed and at least partial reconversion to the parent etioporphyrin takes place. The parent NH compound melts with decomposition at 360–366°

Under strongly basic anhydrous conditions the cleavage of the N-methyl group apparently takes place with even greater ease. Thus, in the presence of CH_3MgI at 100° extensive reversion of the N-methylporphyrin to the porphyrin di-salt occurred. This could be demonstrated by the isolation of the parent porphyrin from the reaction mixture. At 30° this decomposition did not occur and regeneration with acid after determination of the active hydrogens yielded the methylated porphyrin.

We conclude that the phenomenon of steric deformation is illustrated in this compound and is responsible for the observed weakening of the C–N linkage with consequent ready thermal cleavage of the compound. The energy of accommodation to this steric deformation is supplied in such a manner as to shift the absorption spectrum of the compound in the visible in a manner analogous to that observed earlier in the N-methyldipyrrylmethenes. This behavior is in marked contrast with the small effect produced by substitution of methyl for hydrogen on the carbon atoms of the ring.

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Experimental Section

Preparation and Purification of Methylated Etioporphyrin II.—Two grams of etioporphyrin II and 10 cc. of methyl iodide were heated in a sealed tube on a steam cone for twenty-five hours. The reaction takes place at 50°, but seems to be more rapid at 100° At 140° the yield is considerably lower. The tube was opened and the contents poured into 600 cc. of ether in a one-liter separatory funnel. The ether solution was washed once with 10% aqueous sodium hydroxide solution to remove hydrogen iodide, then twice with water. It was extracted with five 100-cc. quantities of 1% hydrochloric acid. The unreacted etioporphyrin II was recovered from the ether by extraction with 5% hydrochloric acid. The 1% extractions were combined, made alkaline with dilute sodium hydroxide, and the porphyrin extracted from the aqueous solution with ether. The ether layer was washed once with water and extracted three or four times with 75 cc. quantities of 0.5% hydrochloric acid. The ether solution was light pink-red in color and contained a small amount of etioporphyrin II. The 0.5% extractions were made alkaline, extracted with ether and, in turn, the ether layer was extracted with 0.5% hydrochloric acid. This second time the total volume of the acid used was 200–250 cc. The deep cherry-red solution was warmed for a few minutes on a steam cone to boil out the ether. The solution was cooled to room temperature. To it five or six drops of perchloric acid were added, whereon a bright pink-red precipitate formed. This was collected by either centrifugation or filtration. The perchlorate was dried in a vacuum desiccator over calcium chloride. The compound decomposed explosively when heated in a flame. The perchlorate weighed 1.48–1.89 g.

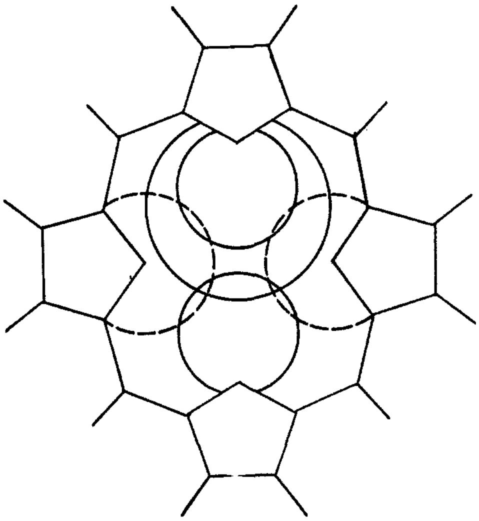

Fig. 1.

To obtain the free base of the methylated porphyrin the perchlorate was suspended in 50–75 cc. of benzene. This solution was shaken with about 50 cc. of a dilute aqueous ammonium hydroxide solution. The benzene layer was separated and dried over anhydrous potassium carbonate. After filtration the benzene solution was passed over a short column of "Alorco" less than 80 mesh activated alumina. The porphyrin was washed through the column with benzene and finally with a small quantity of pure chloroform. The impurities were adsorbed on the alumina.

The red-brown solution was evaporated to dryness in a current of air at room temperature or on a steam cone. The residue from 1.66 g. of the perchlorate weighed 1.38 g. If the perchlorate has one molecule of perchloric acid per molecule of porphyrin, the residue should have weighed 1.38 g.; if two, 1.18 g. Apparently the perchlorate has one molecule of perchloric acid per molecule of porphyrin. The purple solid residue was taken up in 100–150 cc. of acetone. The solution was filtered and 15–20 cc. of distilled water added. This solution was placed in a desiccator over water. After two-three days the larger part of the acetone had distilled over and the methylated porphyrin had crystallized in clusters of deep purple crystals. One to eleven tenths gram (48–53% yield neglecting the recovered etioporphyrin II) of quite pure porphyrin was obtained. More methylated porphyrin of less purity can be isolated from the mother liquor. The crystals were sufficiently pure to be used for studying their chemical reactions and behavior.

To obtain an analytical sample of the methylated porphyrin about 150 mg. of the fairly pure material was dissolved in benzene and the solution passed over activated alumina in a column tall enough to keep the porphyrin adsorbed on the alumina. The band was developed with 1:1 benzene-chloroform. The broad red-violet band in the center of the column was separated from the rest and eluted with pure ethyl ether. The ether solution was evaporated to dryness. The residue was taken up in benzene, passed over a column of Brockmann's alumina and developed in the same manner. At this stage the substance is chromatographically pure. After elution and evaporation under reduced pressure the residue was taken up in purified hexane, and the hexane slowly allowed to evaporate to a small volume. The liquid was poured off and the solid allowed to dry. The crystals were shaken loose from the uncrystallized portion, taken up in methanol and filtered through hardened filter paper. A few cc. of distilled water was added and the solution placed in a desiccator over water. The crystals of methylated porphyrin thus obtained were dried in a high vacuum at room temperature; m. p. 205–210 (dec.).

Anal. Calcd. for etioporphyrin II, $C_{32}H_{38}N_4$; C, 80.29; H, 8.00. Calcd. for N-methyl etioporphyrin II, $C_{33}H_{40}N_4$; C, 80.44; H, 8.18. Found: C, 80.40, 80.46; H, 8.17, 8.21.

Spectra in ether, as observed with wave length spectrometer: Etioporphyrin II, (I) 482–508, (II) 520–535, (III) 565–570, (IV) 620–629 mμ. Methylated etioporphyrin II, (I) 491–515, (II) 530–536, (III) 584–590, (IV) 640–650 mμ.

The compound is exceedingly soluble in all ordinary solvents such as ether, ethyl and methyl alcohols, nitrobenzene, chloroform, carbon tetrachloride, etc.

Its acid number is less than 0.5. The material could not be separated into components by further acid fractionation or by selective adsorption.

The compound remains unchanged on being boiled with alcoholic potassium hydroxide, acetic acid, 50% formic acid or 50% sulfuric acid.

On being held at approximately 210° for about half an hour, the N-methyl group is lost and the compound is reconverted to etioporphyrin II. This is indicated by the shift of the spectrum back to that of etioporphyrin II. The change was proved by comparison of interfacial angles of the crystals on the two-circle goniometer.

Higher Alkylated Derivatives of Etioporphyrin II.—Ethyletioporphyrin II was prepared by treating etioporphyrin II with ethyl iodide in a manner similar to that for preparing methyl etioporphyrin II except that the tube was heated to 135–145° for twenty-five–thirty hours. Longer heating decreased the yield. From 2 g. of the porphyrin about 0.43 g. of perchlorate was isolated and 1.3–1.4 g. of unreacted etioporphyrin II was recovered. The product was purified in the same manner as for the methyl derivative except that an acetone–water mixture was used for the final crystallization.

Anal. Calcd. for $C_{34}H_{42}N_4$: C, 80.59; H, 8.35. Found: C, 80.43; H, 8.49. The spectrum as observed with a wave length spectrometer is identical to that of the methylated derivative.

No reaction could be obtained between etioporphyrin II and *n*-propyl iodide or *n*-butyl iodide.

Oxidation of Etioporphyrin II and Methylated Etioporphyrin II.—Five hundred milligrams of etioporphyrin II was added to 20 cc. of concd. sulfuric acid and the solution stirred at room temperature for twenty-five minutes. Twenty-five grams of crushed ice and a trace of ferrous sulfate were added, and the flask cooled in an ice bath. A solution of 1.7 g. of chromic anhydride in 7 cc. of water and 5 cc. of sulfuric acid was added dropwise over a period of sixty minutes at 3–6°. The solution which was deep green in color was allowed to warm to room temperature and then extracted with ether for eight hours in a Kutscher–Steudel extractor. Solid sodium bicarbonate was added to the ether solution to neutralize the sulfuric acid. The solution was filtered, evaporated and the yellow oil dried over calcium chloride and potassium hydroxide in a vacuum desiccator. The oil crystallized after a few hours. The yield of ethylmethyl maleic imide was 0.23 to 0.26 g. or 39 to 45%.

The solid was hydrolyzed with 20 cc. of 2 *N* sodium hydroxide in a system such that the liberated ammonia was caught in distilled water. Thatcher's test for ammonia was performed and found to be positive. No methylamine was present.[4]

Five hundred milligrams of methylated etioporphyrin II was oxidized in the same way. The yellow oil obtained did not crystallize. The oil was hydrolyzed and a sample of the volatile bases tested for ammonia. In this case the black oily precipitate characteristic of methylamine was formed.[4]

The major portion of the solution of volatile bases was acidified with dilute hydrochloric acid and evaporated to dryness. The white residue was extracted with cold absolute alcohol and the alcoholic solution was filtered and evaporated. The resulting residue was again extracted with absolute alcohol, and the solution filtered and evaporated. In this way the methylamine hydrochloride was separated from ammonium chloride. The methylamine hydrochloride fraction melted at 180–190°; methylamine hydrochloride melts at 227°.

The chloroplatinate of the methylamine fraction was prepared and found to melt with decomposition on long heating at 220–230°. The chloroplatinate prepared from an authentic sample of methylamine shows the same behavior, whereas ammonium chloroplatinate does not melt but decomposes about 350°.

The behavior described above would be characteristic of a mixture of ethylmethylmaleic imide and the N-methyl imide, such as would be formed by the oxidation of both NH and NCH_3 pyrrole rings. To effect separation of the imides, another 500 mg. of methyletioporphyrin II was oxidized and the yellow oil isolated from the ether extraction was dissolved in 1 cc. of toluene and treated with sodium in the manner described for the purification of 1,2,4-trimethyl-3,5-dicarbethoxypyrrole.[5] After the removal of the sodium salt of ethylmethylmaleic imide, the toluene solution of N-methylethylmethylmaleic imide was evaporated and the imide was purified and identified as described by Corwin and Quattlebaum.[4] On hydrolysis and neutralization a pure sample of methylammonium chloride was obtained; m. p. 227°.

Determination of the Number of Active Hydrogens: Method I.—A benzene solution of etioporphyrin II was titrated with a standard solution of sodium triphenyl methyl.[6] The spectrum was observed through a small side arm sealed on the titration flask. Etioporphyrin II possesses a band in the red at 620–630 mμ which is beyond the edge of the absorption region of sodium triphenylmethyl. As the titration proceeds the band becomes fainter and disappears at the end-point. The data gave 2.04 active hydrogens per molecule.

Attempts to determine the number of active hydrogens in the methylated porphyrin failed because a side reaction occurred which gave a substance of such great absorbing power that the spectrum was blanked out.

Method II.—The number of active hydrogens was determined satisfactorily both for the porphyrin and its methylated derivative by reacting at room temperature 5 cc. of 0.1 *N* solution of methylmagnesium iodide in di-*n*-butyl ether with about 0.3 g. of the material. The number of active hydrogen atoms found per molecule was 2.06. This is in good agreement with the result found by titration with sodium triphenylmethyl. With the methylated porphyrin the value found was 1.04.

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[4] Corwin and Quattlebaum, THIS JOURNAL, **58**, 1084 (1936).

[5] Corwin, Bailey and Viohl, *ibid.*, **64**, 1271 (1942).

[6] Corwin and Ellingson, *ibid.*, **64**, 2098 (1942).

The analytical reaction described above was performed at room temperature. When the N-methylated porphyrin was treated with methylmagnesium iodide at 100°, more methane was liberated and part of the porphyrin was converted back to etioporphyrin II, as shown by identification of the porphyrin after its liberation from the magnesium salt by acid. Acid treatment of the magnesium salt of N-methyletioporphyrin II obtained at room temperature, in contrast, yielded unchanged N-methyletioporphyrin II.

Summary

1. N-Methyletioporphyrin II has been prepared and its properties and analysis recorded.

2. The absorption spectrum of this compound shows a shift of all the characteristic porphyrin bands toward the red.

3. Oxidation of the N-methylporphyrin yielded N-methylethylmethylmaleic imide.

4. Thermal decomposition of N-methyletioporphyrin II at its melting point or treatment of it with methylmagnesium iodide at 100° followed by acidification regenerated etioporphyrin II.

5. N-Ethyletioporphyrin II has also been prepared and analyzed.

6. Attempts to prepare N-propyl- and N-butylporphyrins by direct alkylation met with failure.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

The Complexes of Fatty Acids with Amylose[1]

BY F. F. MIKUS, R. M. HIXON AND R. E. RUNDLE

Recent observations by Schoch and Williams[2] that fatty acids interfere with formation of the amylose–iodine complex and selectively precipitate the amylose (unbranched) component of starch have led us to study the interaction between fatty acids and the components of starch. Our interest in this problem arose because it appeared likely that amylose and the fatty acids formed molecular compounds or complexes similar to those which amylose forms with iodine[3] and the alcohols.[3,4] The influence of the tenaciously held fatty materials commonly associated with starch on the physical properties of starch suspensions, pastes and gels is of practical as well as academic interest.

The type of linkage between starch and its "fat-by-hydrolysis" (*i.e.*, that part of the fatty material which cannot be extracted from starch by ether, carbon tetrachloride and the other common fat solvents) has been the subject of several investigations. Early workers were inclined to believe that "fat-by-hydrolysis" was bound to starch by a chemical bond, such as the ester linkage. More recently Schoch[5] has found that "fat-by-hydrolysis" can be extracted from starch almost completely by methanol, 80% dioxane and other hydrophilic fat solvents. By use of solutions of fatty acids in these solvents he was able to reintroduce fatty acids into defatted starches. The reintroduced fatty acids were bound as tightly as "fat-by-hydrolysis", *i.e.*, they were not removed by prolonged carbon tetrachloride extraction, but were removed by methanol. Schoch's work has generally been acknowledged as adequate evidence that the "fat-by-hydrolysis" is not combined by the ester linkage or similar primary chemical bond.

Following the publication of Schoch's work, adsorption has been gaining favor as an explanation of the interaction between starch and "fat-by-hydrolysis."[6,7] The evidence presented below precludes surface phenomena and indicates quite conclusively that the mechanism of starch–fatty acid interaction is similar to that previously advanced for the complexes which amylose forms with iodine and the alcohols.[3,4]

X-Ray Study of the Fatty Acid Complexes

Schoch and Williams[2] have reported that amylose is precipitated by fatty acids in a microcrystalline condition. The crystalline form is unlike that of amylose precipitating from water solution spontaneously, as shown by both optical and X-ray examination. The birefringence of the material is very pronounced. All evidence points to the fact that the fatty acid is contained within the crystalline regions and is responsible for this particular crystalline form of the amylose.

Microscopic observation of the birefringent product of this precipitation indicated that the precipitate was similar to the butanol precipitate of amylose. Since the butanol precipitate has been examined by X-rays,[3d] the most direct way of comparing the fatty acid precipitate with the butanol precipitate appeared to be through X-ray diffraction.

X-Ray Samples and Diagrams.—The method of Schoch and Williams[2] was used to obtain amylose–fatty acid precipitates. Interest in the vari-

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(2) T. Schoch and C. Williams, THIS JOURNAL, **66**, 1232 (1944).

(3) (a) R. Rundle and R. Baldwin, *ibid.*, **65**, 554 (1943); (b) R. Rundle and D. French, *ibid.*, **65**, 558 (1943); (c) *ibid.*, **65**, 1707 (1943); (d) R. Rundle and F. Edwards, *ibid.*, **65**, 2200 (1943); (e) R. Rundle, J. Foster and R. Baldwin, *ibid.*, **66**, 2116 (1944).

(4) R. Bear, *ibid.*, **66**, 2122 (1944).

(5) T. Schoch, *ibid.*, **60**, 2824 (1938).

(6) L. Lehrman, *ibid.*, **64**, 2144 (1942).

(7) R. Whistler and G. Hilbert, *ibid.*, **66**, 1721 (1944).