constant m. p. (147.0–147.5°). Calcd.: C, 76.57; H, 6.43. Found: C, 76.81; H, 6.61.

Acknowledgment.—The authors wish to thank the Research Corporation for a grant-in-aid supporting this project.

Summary

Methyl malonic ester has been shown to add to the 1-position of 3,4-dihydronaphthalene-1,2-oxide, yielding α-1-(1,2,3,4-tetrahydronaphthol-2)-propionic acid lactone (*trans*). This lactone may also be obtained from 2-bromo-1,2,3,4-tetrahydronaphthol-1 and methyl malonic ester.

The theoretical implications of this result are discussed.

HOLLAND, MICHIGAN RECEIVED OCTOBER 20, 1949

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

1,4,5,8-Tetramethyl-2,3,6,7-tetracarbethoxyporphyrin and Some Derivatives[1]

BY JOHN S. ANDREWS,*[2] ALSOPH H. CORWIN† AND ALVIN G. SHARP[3]

One of the most readily available pyrrole derivatives is 2,4-dimethyl-3,5-dicarbethoxypyrrole. Its conversion into a porphyrin should yield an easily prepared synthetic porphyrin. Several unsuccessful attempts to achieve this[4] have led certain investigators to the conclusion that carbethoxy groups hinder porphyrin formation.

Observations made in our studies of the mechanism of the aldehyde synthesis of dipyrrylmethenes[5] have led to the discovery of a unique porphyrin synthesis which proceeds smoothly at room temperature and yields the crystalline product directly from the reaction medium. The fact that a porphyrin containing four carbethoxy groups can be prepared readily suggests that previous assumptions regarding their influence on porphyrin formation can no longer be justified.

The success of the method depends upon two reactions which have been shown to exist when the N-methylpyrryl aldehyde I is condensed with the α-unsubstituted pyrrole II. The first is the formation of the tripyrrylmethane intermediate III and the second is the specific cleavage of this intermediate at the bond attaching the N-methylpyrryl group to the methane carbon (Chart I).

This reaction is comparable in effect to the formic acid condensation frequently employed for the synthesis of symmetrical dipyrrylmethenes in that the N-methylpyrryl aldehyde appears to serve solely as the source of the carbon joining the two pyrrole groups in the methene IV. Unlike the formic acid method, however, the reaction above proceeds quantitatively.

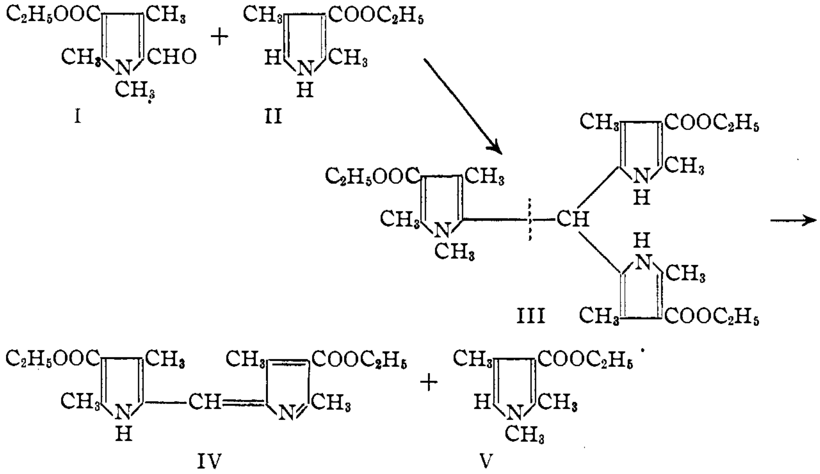

CHART I

These observations led to the prediction that substitution of a 5,5′-unsubstituted dipyrrylmethane VI for the α-unsubstituted pyrrole II should lead to the coupling of two molecules of the methane yielding the methene VII. This in turn should condense to the dihydroporphyrin VIII which should oxidize spontaneously to the porphyrin IX (Chart II).

The reaction has been carried out and the predictions realized by the isolation of the crystalline porphyrin. The high acid number of the porphyrin is of the magnitude expected for this type of material.

The complicated series of transformations necessary for the formation of the porphyrin is not

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* Harvard University A.M. 1927.

† Harvard University Ph.D. 1932.

[1] Porphyrin Studies, VIII. For previous porphyrin studies in this series see Corwin and Krieble, THIS JOURNAL, **63**, 1829 (1941); Corwin and Buc, *ibid.*, **66**, 1151 (1944); McEwen, *ibid.*, **68**, 711 (1946); Ellingson and Corwin, *ibid.*, **68**, 1112 (1946); Erdman and Corwin, *ibid.*, **68**, 1885 (1946); Corwin and Erdman, *ibid.*, **68**, 2473 (1946); Erdman and Corwin, *ibid.*, **69**, 750 (1947).

[2] Present address: General Mills Research Laboratories, Minneapolis, Minn.

[3] Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

[4] Fischer, *et al.*, *Ann.*, **452**, 270, 273 (1927); **448**, 194, note 1 (1926); **473**, 236 (1929).

[5] Corwin and Andrews, THIS JOURNAL, **58**, 1086 (1936).

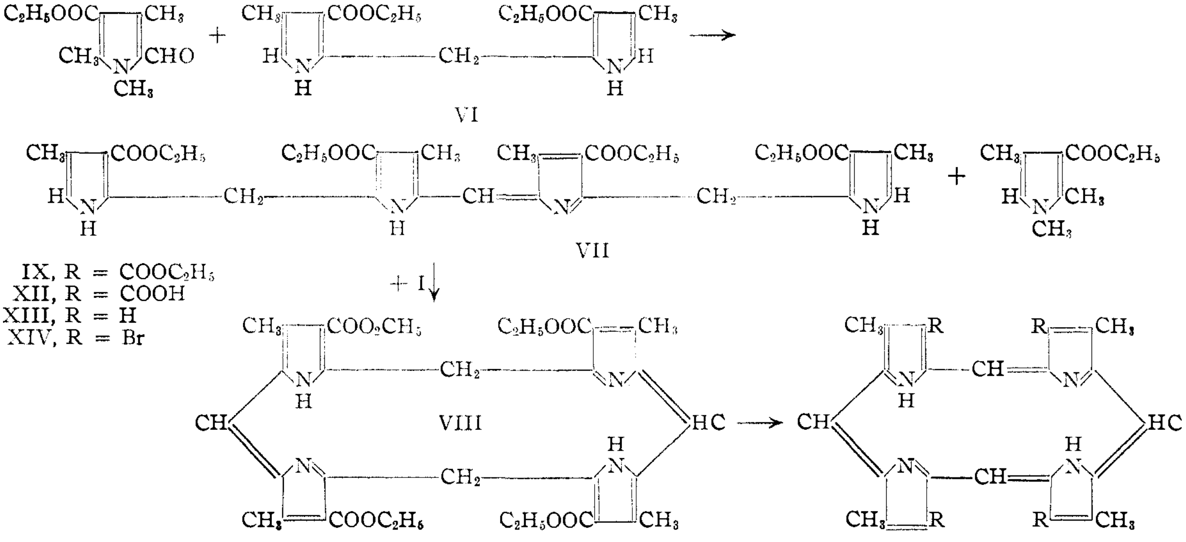
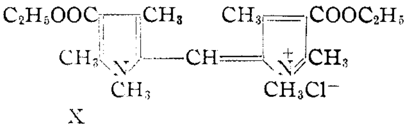


CHART II

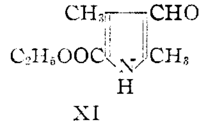
conducive to high yields and in view of the numerous reaction possibilities the 40% yield obtained under best conditions is quite satisfactory. Several other reaction products have been isolated in quantities which almost completely account for the reagents used. One reaction product is a red crystalline material which was first assumed to be methene VII. Isolated as the hydrochloride, it rapidly lost its brilliant color and darkened in the air. Converted to the free base, it is a beautifully crystalline orange-red compound. Under certain conditions nearly quantitative yields can be obtained. The simultaneous isolation of considerable quantities of N-methylpyrrole (V) indicates that there is no N-methylpyrryl substituent. From analytical data this substance appears to be a dehydrogenation product of methene VII but the light color does not seem consistent with this assumption.

Attempts to deduce further evidence for its structure by examining quantitative differences arising from variation of the relative amounts of reagents revealed the presence of a secondary reaction. The reaction scheme requires one mole of the pyrryl aldehyde and two moles of the dipyrrylmethane for the formation of the methene VII.[6] Actually, the highest yield resulted from the use of equimolecular quantities. At the same time this increase of aldehyde led to increased coloration of the reaction medium. The reaction responsible for this phenomenon is the condensation of aldehyde I with pyrrole V to form the di-N-methylmethene X. For the same reason an excess of aldehyde over the equimolar amount required in the scheme serves to increase the yield of porphyrin.

Two methods earlier found satisfactory for the isolation of tripyrrylmethanes[5] were tried here in the hope of isolating the tripyrrylmethane type intermediate between VI and VII. These methods were the condensation with dilute acid and the Feist fusion method. Neither yielded the desired intermediate. With dilute acid, the original materials were recovered unchanged. Direct fusion brought about decomposition. In addition, condensation with potassium acid sulfate was tried. This led to a reaction at even lower acidity than that with hydrogen chloride but cleavage took place simultaneously. This was evidenced not only by the appearance of the characteristic odor of the N-methyl-α-unsubstituted pyrrole V but also by the isolation of small quantities of porphyrin IX. This is the condensation yielding porphyrin under the mildest conditions of acidity, but the yields are less satisfactory than those obtained with hydrogen chloride and greater difficulties attend the isolation.



X



XI

It has also been observed that porphyrin IX may be obtained from methane VI by the use of formic acid, but as in the case of the simple methene condensation,[5] the yields are not as satisfactory as those obtained with the N-methyl aldehyde. The β-pyrryl aldehyde XI may also be used as a source of the bridge carbon.

Porphyrin IX may be hydrolyzed to the free acid XII by the use of potassium hydroxide in ethylene glycol at 200°. Decarboxylation of the potassium salt of the acid takes place at the boil-

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[6] Brunings and Corwin, THIS JOURNAL, 64, 593 (1942).

ing point of anhydrous glycerol with the production of 1,4,5,8-tetramethylporphyrin XIII, which can be brominated to the tetrabromo derivative, XIV.

The authors wish to acknowledge a grant-in-aid from the Rockefeller Foundation which permitted the investigation of this condensation.

Experimental

3,3′-Dicarbethoxy-4,4′-dimethyl-5,5′-dicarboxydipyrrylmethane.—For the preparation of the porphyrin, the dipyrrylmethanedicarboxylic acid must be of greater purity than that obtained by the caustic hydrolysis used by Fischer and Halbig.[7] A purer product was obtainable when carbonate was used for the hydrolysis. Twenty grams of 3,5,3′,5′-tetracarbethoxy-4,4′-dimethyldipyrrylmethane[8] was dissolved in 100 cc. of ethanol and refluxed for thirty-six hours with 18 g. of potassium carbonate in 100 cc. of water. After the first day, 200 cc. of water was added. After refluxing, the solution was diluted with 400 cc. of water and filtered. The filtrate was acidified with acetic acid and filtered. The gelatinous residue was placed in suspension in 250 cc. of water and about 4 g. of sodium hydroxide added to complete solution of the acid. Hot saturated sodium chloride was added to precipitate the sodium salt. After cooling, this was filtered, the residue acidified with warm dilute hydrochloric acid, filtered and washed with hot water. The acid was dried at 100°. Eight grams of the acid was obtained (46%).

3,3′-Dicarbethoxy-4,4′-dimethyldipyrrylmethane (VI).[7]—Eight grams of purified dipyrrylmethanedicarboxylic acid was thoroughly mixed with 30 cc. of dry glycerol (obtained by heating to 290° and cooling) in a 500-cc. boiling flask equipped with a Hershberg stirrer and inlet tube of nitrogen. The flask and contents were rapidly heated to 220–230°, then slowly to 250° at which point carbon dioxide evolution had practically ceased. The decarboxylation should be completed in less than five minutes. The material was allowed to cool slightly and 60 cc. of alcohol was added to complete the cooling and to dissolve the material. The solution was allowed to stand in the ice-box overnight, filtered and recrystallized from ethanol and water. The product was dissolved in boiling absolute ether (peroxide free and dry), norite was added and removed by filtration, the filtrate evaporated until crystals started to form and peroxide free hexane was added. White crystals were obtained, m. p. 188° (Fischer and Halbig[7] report 173°). The yield after purification was 2 g. or 32%.

1,4,5,8-Tetramethyl-2,3,6,7-tetracarbethoxyporphyrin (IX). **Condensation** (a).—One gram of 3,3′-dicarbethoxy-4,4′-dimethyldipyrrylmethane and 1.28 g. of 1,2,4-trimethyl-3-carbethoxy-5-formylpyrrole (I) were dissolved in 150 cc. of absolute ether and the system was saturated with dry hydrogen chloride at 0°. The flask was stoppered tightly and allowed to stand for ten days in the dark at room temperature.

Condensation (b).—One gram of the dipyrrylmethane and 1 g. of the N-methyl aldehyde were fused in a test-tube in an oil-bath at 160° and a small amount of finely powdered potassium acid sulfate added. After fifteen minutes at 160°, the fusion mixture was transferred to a flask by dissolving in 200 cc. of dry ether. The solution was saturated in the cold with dry, gaseous hydrogen chloride, allowed to warm slowly to room temperature and then allowed to stand overnight.

Isolation and Purification.—The suspension was filtered to remove the red "polymethene" and the filtrate evaporated to dryness. The residue from the evaporation was washed alternately with 200 cc. of water and 200 cc. of ether, transferring the washings to a separatory funnel. The ether layer was washed with water until the washings were colorless. The precipitate in the ether was filtered, suspended in 20–30 cc. of chloroform and two volumes of methanol added to precipitate dissolved porphyrin. The "polymethene" was extracted with chloroform until free from porphyrin, the extract evaporated to 20–30 cc., the porphyrin precipitated with two volumes of methanol and removed by filtration. Alternatively, the extraction of the "polymethene" can be made with dry ether containing hydrogen chloride, the extract dried and crystallized from chloroform and methanol; yield (a) 150–420 mg., (b) 50–150 mg.

Anal. Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.04; H, 5.85. Found: C, 65.91; H, 5.90. Absorption bands in the hand spectroscope: I, 510–528 mμ; II, 550–560 mμ; III, 590–600 mμ; IV, 645–650 mμ; order of intensity: I, IV, II, III.

The acid number has not been determined with precision but is near 25.

More than forty experiments have been carried out in attempts to find optimum reaction conditions. Ether was the best solvent tried, since a high concentration of hydrogen chloride appears to be necessary for the condensation. Ice temperatures gave higher yields of "polymethene" which does not appear to be an intermediate. Excess aldehyde increases the yield by combining with the 1,2,4-trimethyl-3-carbethoxypyrrole formed in the cleavage. Equimolar proportions give less porphyrin.

Condensation of 120 mg. of the dipyrrylmethane with 4.5 cc. of 100% formic acid for fifteen minutes at 40° using 2.5 g. of *p*-toluenesulfonic acid as catalyst and 6 cc. of ether as solvent gave a yield of approximately 8 mg. of porphyrin estimated as 50% pure. Many other reaction conditions using formic acid gave poorer yields of porphyrin.

Condensations were also performed using 2,4-dimethyl-3-formyl-5-carbethoxypyrrole as the source of the bridge carbons. The yields were comparable to those obtained with the N-methyl aldehyde.

The aqueous washings from the ether suspension of the porphyrin contain 1,3,5,1′,3′,5′-hexamethyl-4,4′-dicarbethoxydipyrrylmethane. Neutralization of the solution destroys the color and yields a gummy precipitate of the carbinol. This may be purified through the methene perchlorate by the method of Brunings and Corwin.[6] After purification and crystallization, the carbinol melts at 142°.

In attempts to isolate the tripyrrylmethane type intermediate in porphyrin formation, condensations were run using 640 mg. of the dipyrrylmethane and 410 mg. of the N-methyl aldehyde, following the procedures of Corwin and Andrews[9] using traces of hydrogen chloride at room temperature and using potassium bisulfate at 150°. In neither case could the intermediate be isolated, but the latter condensation yielded a small amount of porphyrin.

"Polymethene" By-product.—Six hundred and forty milligrams of the dipyrrylmethane and 410 mg. of the N-methyl aldehyde were dissolved in 60 cc. of dry ether, cooled in an ice-bath and saturated with dry hydrogen chloride. The mixture was allowed to stand at 0° overnight. The "polymethene" was then isolated as described in the preceding section; yield about 500 mg. The free base was prepared by the method of Corwin and Andrews.[9] It is soluble in cold chloroform, sparingly soluble in hot toluene and insoluble in hexane. It may be recrystallized from chloroform and hexane or from toluene. The crystals are orange colored and the solutions yellow.

Anal. Calcd. for $C_{36}H_{42}O_8N_4$: C, 65.00; H, 6.55. For $C_{35}H_{38}O_8N_4$: C, 65.41; H, 5.96. Found: C, 65.41, 65.37; H, 6.05, 6.18.

Attempts to convert this material into porphyrin by further condensation with N-methyl aldehyde yielded no trace of porphyrin. It does not seem probable that the material is an intermediate in the synthesis, perhaps because of improper steric configuration.

1,4,5,8-Tetramethyl-2,3,6,7-tetracarboxyporphyrin (XII).—One hundred milligrams of tetramethyltetra-

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[7] Fischer and Halbig, *Ann.*, **447**, 133 (1926).

[8] Corwin, Bailey and Viohl, This Journal, **64**, 1267 (1942).

[9] Corwin and Andrews, *ibid.*, **59**, 1973 (1937).

carbethoxyporphyrin and 100 mg. of potassium hydroxide were suspended in 25 cc. of ethylene glycol. The mixture was heated in a metal-bath at 200° for five hours, then cooled and diluted with water. The solution was acidified with 0.4 cc. of concentrated hydrochloric acid and the porphyrin removed by filtration, dried, dissolved in hot pyridine and precipitated with three volumes of methanol. On cooling, 55 mg. of impure porphyrin was obtained. This was purified for analysis by repetition of the pyridine, methanol treatment and then by crystallization from a chloroform–methanol mixture.

Anal. Calcd. for $C_{28}H_{22}O_8N_4$: C, 61.99; H, 4.09. Found: C, 62.12; H, 4.25.

1,4,5,8-Tetramethylporphyrin (XIII). (a) **From Tetramethyltetracarbethoxyporphyrin.**—About 5 cc. of anhydrous glycerol was heated in a metal-bath to 290° and 0.1 g. of potassium hydroxide and 100 mg. of tetramethyltetracarbethoxyporphyrin added. The air was displaced by nitrogen and the mixture stirred occasionally. After two hours an additional 0.1 g. of potassium hydroxide and 3–4 cc. of glycerol were added and the mixture heated for another hour. It was then cooled, diluted with 100 cc. of water and filtered. The residue was dissolved in 40 cc. of chloroform and 50 cc. of methanol added. The yield was 38 mg. (67.5%) of crystalline porphyrin.

Anal. Calcd. for $C_{24}H_{22}N_4$: C, 78.66; H, 6.05. Found: C, 78.58; H, 5.98.

(b) From **Tetramethyltetracarboxyporphyrin.**—About 20 mg. of crude tetramethyltetracarboxyporphyrin was heated in glycerol with 0.1 g. of potassium hydroxide for two and a half hours at 290° and then isolated as described above. Less than a milligram of material was obtained.

1,4,5,8-Tetramethyl-2,3,6,7-tetrabromoporphyrin (XIV).—Twenty-five milligrams of tetramethylporphyrin was dissolved in 100 cc. of hot chloroform and to this was added about 100 mg. of bromine in chloroform. A precipitate soon appeared and methanol was added to complete its separation. The porphyrin was collected on a filter paper and crystallized from 75 cc. of hot nitrobenzene. Long, needle-like crystals appeared on cooling. These were collected and washed with chloroform; yield 39 mg. or 84%.

Anal. Calcd. for $C_{24}H_{18}N_4Br_4$: C, 42.26; H, 2.66. Found: C, 42.35; H, 2.80.

Summary

1. A new porphyrin condensation, proceeding at room temperature, has been recorded.

2. This condensation gives relatively good yields of 1,4,5,8-tetramethyl-2,3,6,7-tetracarbethoxyporphyrin, a type of porphyrin not available with earlier synthetic methods.

3. Derivatives of this porphyrin have been prepared.

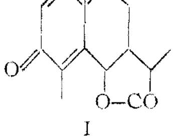
BALTIMORE 18, MD. RECEIVED SEPTEMBER 30, 1949

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis and Rearrangement of Cyclohexadienones

BY R. B. WOODWARD* AND TARA SINGH†

Cyclohexadienones were first prepared, and many of their remarkable properties were first observed, in the course of von Auwers' classical studies on the nature of the neutral products formed through the action of chloroform and alkalies on *o*- and *p*-substituted phenols.[1] Subsequently, the establishment of the presence of a cyclohexadienone ring in the natural product santonin (I),[2] and the use of cyclohexadienone intermediates in the aromatization of ring A of the sterol nucleus,[3] engendered renewed interest in the chemical properties of cyclohexadienones, and in methods for their synthesis. Cyclohexadienones have been prepared from phenols by von Auwers' methods, from cyclohexanones by bromination and dehydrohalogenation, and by a ring-synthetic method suggested by Paranjpe, and reduced to practice by Wilds and Djerassi[4] (*vide infra*).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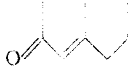
II

In this communication, we describe a new synthetic method which we have used for the synthesis of 10-methyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene (II) and demonstrate the nature of the rearrangement which this ketone undergoes under the influence of acidic reagents. The synthetic method is in effect an extension of the well-known method introduced by Robinson for the construction of polycyclic cyclohexenones by condensation of a cyclic ketone with methyl vinyl ketone, or a suitable progenitor of the latter.[5] Thus, we have found that when the sodium derivative of 2-methylcyclohexanone is condensed with methyl ethinyl ketone, the ketone (II) is produced directly, though in low yield. Pure 10-methyl-2-keto-$\Delta^{1,9;3,4}$-hexahydronaphthalene is a liquid, b. p. 123–124° (3 mm.); it was characterized by the preparation of a crystalline red dinitrophenylhydrazone, m. p. 127–129°, and through its infra-

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* Harvard University 1937–.

† Harvard University 1948–.

(1) von Auwers and v. Erggelet, *Ber.*, **32**, 3598 (1899); v. Auwers and Winternitz, *ibid.*, **35**, 465 (1902); v. Auwers and Keil, *ibid.*, **35**, 4207 (1902), and many subsequent papers.

(2) Clemo, Haworth and Walton, *J. Chem. Soc.*, 1110 (1930).

(3) Inhoffen and Huang-Minlon, *Naturwissenschaften*, **26**, 756 (1938); Inhoffen, Zühlsdorff and Huang-Minlon, *Ber.*, **73**, 451 (1940); Inhoffen, *Angew. Chem.*, **53**, 473 (1940); Inhoffen and Zühlsdorff, *Ber.*, **74**, 604, 1911 (1941); Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946); Inhoffen, *Angew. Chem.*, **59A**, 207 (1947); Djerassi and Scholz, THIS JOURNAL, **70**, 1911 (1948); Inhoffen and Stoeck, *Ann.*, **563**, 127 (1949); Inhoffen, Stoeck and Lübcke, *ibid.*, **563**, 177 (1949).

(4) Wilds and Djerassi, THIS JOURNAL, **68**, 1716 (1946).

(5) du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and many subsequent papers.