34. *Pyrroles and Related Compounds. Part II.* Michael Addition to Pyrromethenes.*

By A. C. JAIN and G. W. KENNER.

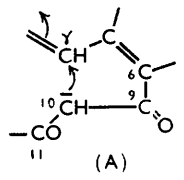
In connection with a speculation about the biosynthesis of chlorophyll, the Michael addition of cyanoacetic ester to pyrromethenes (I) has been studied. Usually the adduct (II) is degraded to the ethyl α-cyano-β-2-pyrrolylacrylate (III), but its general structure is preserved in one product (IV; X = CN).

FISCHER commented on the close structural relation between chlorophyll *a* and hæmin; apart from the presence of magnesium and the esterifying phytyl and methyl residues in chlorophyll *a*, it differs from hæmin in possessing (1) two hydrogen atoms at positions 7 and 8, being a chlorin, (2) a carbonyl group at position 9, (3) an isocyclic ring, and (4) an ethyl, instead of a vinyl, group at position 4. Regarding hæmin as the biologically more fundamental pigment, he envisaged the following formal transformations of protoporphyrin IX:[1] " Oxydiert man die in 6-Stellung befindliche Propionsäure in β-Stellung zur Ketopropionsäure, versetzt die beiden Wasserstoffatome von 9 an Stellung 7 und 8, führt dehydrierenden Ringschluss von C-10 zur γ-Methinbrücke aus und verlagert diese beiden Wasserstoffatome an die Vinylgruppe in 2 (*sic*), so entsteht die Formel für Phäophorbid *a*." Meantime the common origin of the two pigments from porphobilinogen

* Part I, *J.*, 1958, 3779. Some of the material in the present paper was presented to the XVIth International Congress of Pure and Applied Chemistry, Paris, 1957.

[1] Fischer and Stern, " Chemie des Pyrrols," Akademische Verlag, Leipzig, 1940, Vol. II, Part 2, pp. 37—38.

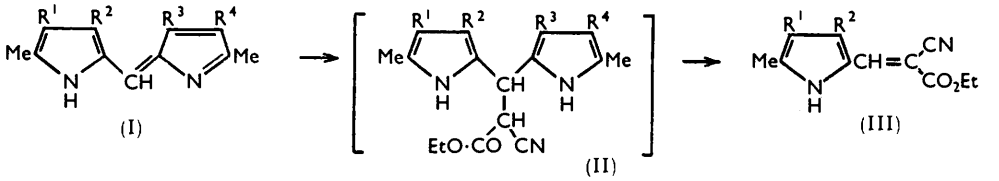
and protoporphyrin has been established experimentally.[2] The route from protoporphyrin to chlorophyll *a* is believed to pass through magnesium 2-vinylphæoporphyrin-a_5,[3] which already possesses structural features (2), (3), and (4) as well as the esterifying methyl group. Probably feature (1) and the phytyl group are added successively after this stage.[4] As to the steps preceding it, β-oxidation of the propionic acid side-chain, covering feature (2), has a reasonable analogy in the aliphatic series, and it has been advanced [5] as a plausible mechanism for the decarboxylation of the side-chains, which appear as vinyl groups in protoporphyrin, at positions 2 and 4 in uroporphyrin III. We now suggest that either the methyl ester or the coenzyme A derivative of this keto-acid would be disposed, when ionised or enolised, towards closure of the isocyclic ring by a change of the Michael type (A).



(A)

The electrons displaced from the γ-methine group would have to be accepted by either an oxidising agent or a conjugated double bond, as in the ordinary Michael reaction. If the biochemical evidence that saturation of the 7 : 8-double bond takes place independently is accepted, it is tempting to follow Fischer's formal scheme connecting saturation of the vinyl group with closure of the isocyclic ring. However this may be, it is in our opinion worthwhile striving to prepare the appropriate β-keto-acid derivatives for both chemical and biochemical studies. As a preliminary task, the reactivity of the more accessible pyrromethenes has been studied, since they can be regarded as crude models of half the porphyrin molecule or rather its magnesium complex, which is more probably involved in the cyclisation.

The behaviour of the readily accessible 4 : 4′-diethyl-3 : 5 : 3′ : 5′-tetramethylpyrromethene (I; $R^1 = R^4 = Et$, $R^2 = R^3 = Me$) with malonic, acetoacetic, and cyanoacetic esters under the usual conditions of Michael reactions was examined. Only cyanoacetic ester was sufficiently reactive and, whether basic or acidic catalysis was used, the isolated product was a yellow crystalline substance, identical with a synthetic sample of ethyl α-cyano-β-(4-ethyl-3 : 5-dimethyl-2-pyrrolyl)acrylate (III; $R^1 = Et$, $R^2 = Me$). Mechanisms in accordance with the usual electronic theory can easily be written to account for formation of an adduct (II) and its decomposition to the yellow product (III); under acidic conditions the pyrromethene would be in the more reactive form of its hydrochloride. Moreover, there are numerous analogies for decomposition of the hypothetical adduct with ejection of a pyrrole residue.[6] It is likely that some of the colourless adduct (II) was present in the substantial uncrystallised residue from the reaction under basic catalysis, but most of the material from the acidic reaction was accounted for as recovered starting



(I) (II) (III)

material or the yellow product. A similar yellow compound (III; $R^1 = Me$, $R^2 = H$) was obtained likewise from an unsymmetrical pyrromethene (I; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = Et$). As the fragment eliminated here from the presumed intermediate

[2] Rimington, *Ann. Rev. Biochem.*, 1957, **26**, 572.

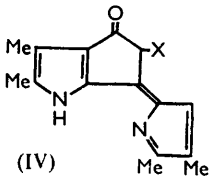
[3] Granick, "Chemical Pathways of Metabolism" (ed. Greenberg), Academic Press, New York, 1954, Vol. II, p. 287; "Porphyrin Biosynthesis and Metabolism" (ed. Wolstenholme and Millar), Churchill, London, 1955, p. 143.

[4] Wolff and Price, *Arch. Biochem. Biophys.*, 1957, **72**, 293.

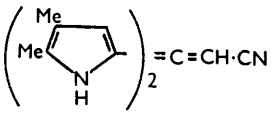
[5] MacDonald, "Porphyrin Biosynthesis and Metabolism" (ed. Wolstenholme and Millar), Churchill, London, 1955, p. 155.

[6] *E.g.*, Fischer and Ammann, *Ber.*, 1923, **56**, 2319; Corwin and Andrews, *J. Amer. Chem. Soc.*, 1936, **58**, 1086; 1937, **59**, 1973; Paden, Corwin, and Bailey, *ibid.*, 1940, **62**, 418; Treibs, Herrmann, Meissner, and Kuhn, *Annalen*, 1957, **602**, 153.

(II; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = Et$) was 3-ethyl-2 : 4-dimethylpyrrole, just as in the former instance, it seemed that decomposition of the adduct might have been encouraged by substituents in the 4- and the 4'-position, and therefore the adduct (II; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) might actually be obtained from another symmetrical pyrromethene (I; $R^1 = R^4 = Me$, $R^2 = R^3 = H$). However, once more the decomposition product (III; $R^1 = Me$, $R^2 = H$), identical with that from the unsymmetrical pyrromethene, was produced under both basic and acidic conditions, but from the former reaction a second, red crystalline product was isolated. Apparently this substance, to which we assign structure (IV; X = CN), arises from the adduct (II; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) through condensation between the ester group and the neighbouring free β-position and dehydrogenation by another molecule of pyrromethene. Its absorption of visible and ultraviolet light resembles that of pyrromethenes, for example the starting material (I; $R^1 = R^4 = Me$, $R^2 = R^3 = H$), while the infrared spectrum shows in addition bands at 2200 and 1713 cm.$^{-1}$ corresponding to the nitrile and the cyclic carbonyl group. The expected position of the latter can only be conjectured, the opposing influences of ring-strain and of conjugation with the pyrrole nucleus being borne in mind, but it is noteworthy that absorption by chlorophyll derivatives at 1700 cm.$^{-1}$ has been ascribed to the rather similarly situated cyclic carbonyl group.[7] Attack on the nitrile group appeared to be hindered sterically, but the amide (IV; $X = CO{\cdot}NH_2$) was formed by warm 85%



(IV)



(V)

sulphuric acid and its absorption spectra confirmed the structure (IV). Alkaline hydrolysis of the nitrile removed the carbonyl group, producing a yellow crystalline material. Although we lack a sample synthesised by another route for comparison because di-(4 : 5-dimethyl-2-pyrrolyl) ketone does not have normal carbonyl properties (cf. spectral data in Experimental section), we regard structure (V) as justified by the analytical and spectral data and as supporting the assignment of structure (IV; X = CN) to the precursor.

Viewed in the broadest way, our results merely extend the published evidence, provided especially by the work of Corwin and his colleagues,[6,8] that the methine bridge of pyrromethenes has considerable cationoid reactivity, but we think that they make the hypothesis expounded in the first paragraph more plausible by providing closer analogies. Still better would be studies of pyrromethenes bearing the β-diketo-side-chain, but we have not yet succeeded in preparing such compounds. Studies in the porphyrin series are in progress.

Experimental

Ethyl α-Cyano-β-(4-ethyl-3 : 5-dimethyl-2-pyrrolyl)acrylate (III; $R^1 = Et$, $R^2 = Me$).—3-Ethyl-5-formyl-2 : 4-dimethylpyrrole was conveniently prepared in 90% yield from 3-ethyl-2 : 4-dimethylpyrrole by the phosphoryl chloride–dimethylformamide reaction.[9] A solution of the aldehyde (1·5 g.), ethyl cyanoacetate (1·1 c.c.), ammonium acetate (0·2 g.), and glacial acetic acid (0·1 c.c.) in benzene was boiled vigorously during 3 hr. while water was drawn off through a Vigreux fractionating column fitted with a Dean–Stark head.[10] The residue from evaporation of the benzene was extracted with boiling *n*-hexane which, on being cooled, deposited lemon-yellow needles (1·4 g.) of the product, m. p. 123—124° (ref. 11 records m. p.

[7] Weigl and Livingston, *J. Amer. Chem. Soc.*, 1953, **75**, 2173.
[8] Brunings and Corwin, *ibid.*, 1944, **66**, 337; Corwin and Doak, *ibid.*, 1955, **77**, 464.
[9] Chu and Chu, *J. Org. Chem.*, 1954, **19**, 266; Smith, *J.*, 1954, 3845.
[10] Cf. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3453.
[11] Fischer and Neber, *Annalen*, 1932, **496**, 12.

121°), absorption maxima in ethanolic solution at 309, 403 mμ (log ε 3·58, 4·64 respectively) and in Nujol mull at 2215, 1710, 1595, 1550 cm.$^{-1}$.

Ethyl α-Cyano-β-(4 : 5-dimethyl-2-pyrrolyl)acrylate (III; R^1 = Me, R^2 = H).—2 : 3-Dimethylpyrrole was prepared by the published method,[12] except that hydrolysis and decarboxylation were carried out separately in boiling dilute sodium hydroxide solution (4 hr.) and in 2-aminoethanol at 160° (1 hr.), and it was converted into 2-formyl-4 : 5-dimethylpyrrole by the phosphoryl chloride–dimethylformamide reaction[9] (75% yield). Condensation of the aldehyde and ethyl cyanoacetate, as in the foregoing preparation, afforded small needles, m. p. 184—185°, of the *product* (Found: C, 66·0; H, 6·5; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·5; N, 12·8%), absorption maxima in ethanolic solution at 213, 293, 405 mμ (log ε 3·88, 3·01, 4·71 respectively) and in Nujol mull at 2190, 1700, 1590, 1552 cm.$^{-1}$.

Reactions between 4 : 4′-Diethyl-3 : 5 : 3′ : 5′-tetramethylpyrromethene (I; R^1 = R^4 = Et, R^2 = R^3 = Me) *and Ethyl Cyanoacetate.*—3-Ethyl-2 : 4-dimethylpyrrole was prepared from ethyl 4-acetyl-3 : 5-dimethylpyrrole-2-carboxylate in 80—85% yield by successive hydrogenation with Raney nickel catalyst,[13] alkaline hydrolysis, and acidic decarboxylation in preference to the previously recommended single operation.[14] The derived pyrromethene,[15] m. p. 148—149°, showed absorption maxima in ethanolic solution at 225, 328, 447 mμ (log ε 4·01, 3·53, 4·55 respectively).

A solution of the pyrromethene (1 g.) in freshly distilled ethyl cyanoacetate (5 c.c.) was heated with triethylamine (0·3 c.c.) at 100—105° during 2 hr. The residue from evaporation of the excess of ester under reduced pressure was extracted with boiling light petroleum (b. p. 60—80°), which left a dark tar. When the extract was percolated through a column of animal charcoal, concentrated, and cooled, it deposited ethyl α-cyano-β-(4-ethyl-3 : 5-dimethyl-2-pyrrolyl)acrylate (0·2 g.), identical with material prepared by the previously described method.

A similar experiment, in which the initial solution was saturated with dry hydrogen chloride and triethylamine was omitted, yielded the same product (0·1 g.), and starting material was recovered from the extracted residue by dissolution in ethanol and neutralisation with a few drops of aqueous ammonia solution.

Reactions between 4-Ethyl-3 : 5-4′ : 5′-tetramethylpyrromethene (I; R^1 = R^4 = Me, R^2 = H, R^4 = Et) *and Ethyl Cyanoacetate.*—The hydrobromide of the pyrromethene was prepared by Heidelmann's route,[16] and it was converted into the free base, m. p. 300° (decomp.), by shaking its solution in chloroform with lime water. The reaction with ethyl cyanoacetate and triethylamine, carried out as in the foregoing example, yielded ethyl α-cyano-β-(4 : 5-dimethyl-2-pyrrolyl)-acrylate (0·18 g.), identical with material prepared by the previously described method. The same product (0·085 g.) was obtained by acidic catalysis of the reaction.

Reactions between 4 : 5 : 4′ : 5′-Tetramethylpyrromethene and Ethyl Cyanoacetate.—The pyrromethene,[12] m. p. 115—116°, showed absorption maxima in solution in dioxan at 223, 308, 438 mμ (log ε 3·98, 3·65, 4·47 respectively) and in Nujol mull at 3480—3300 w, 1620 s, 1565 cm.$^{-1}$. Its acid-catalysed reaction with ethyl cyanoacetate yielded ethyl α-cyano-β-(4 : 5-dimethyl-2-pyrrolyl)acrylate (0·10 g.) as in the foregoing experiments.

A mixture of the pyrromethene (1 g.), triethylamine (0·35 c.c.), and ethyl cyanoacetate (5 c.c.) was kept between 100° and 105° during 2 hr.; red crystals began to separate after 1 hr. The usual procedure then furnished 0·15 g. of the same yellow product as obtained by acidic catalysis. The red crystalline residue (0·1 g.) from the extraction with light petroleum was recrystallised from ethyl acetate and sublimed at 220—230°/0·01 mm. in clusters of red needles, m. p. 279—280°; this cyano-ketone {*5-cyano-6-(4 : 5-dimethyl-2H-pyrrolylidene)-1 : 4 : 5 : 6-tetrahydro-2 : 3-dimethyl-4-oxocyclopenta*[b]*pyrrole*} (IV; X = CN) (Found: C, 72·1; H, 5·6; N, 15·8. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%) showed absorption maxima in ethanolic solution at 242, 318, 445 mμ (log ε 4·00, 3·90, 4·61 respectively) and in Nujol or hexachlorobutadiene mulls at 3310 s, 3100 w, 2930 w, 2860 w, 2200 s, 1713 s, 1598 s, 1515 s, 1463 w, 1363, 1337 w, 1272 s, 1245, 1222, 1157, 1067, 1020 w, 975, 854, 800, 752 s, 716 cm.$^{-1}$.

This cyano-ketone (IV; X = CN) was recovered unchanged from attempted reactions with concentrated hydrochloric acid diluted with 2 vols. of ethanol (2 hr. at 100°) and with hydrogen

[12] Corwin and Krieble, *J. Amer. Chem. Soc.*, 1941, **63**, 1831.
[13] Signaigo and Adkins, *ibid.*, 1936, **58**, 710.
[14] Fischer, *Org. Synth.*, 1941, **21**, 67.
[15] Fischer, Halbig, and Walach, *Annalen*, 1927, **452**, 297.
[16] Fischer and Orth, "Chemie des Pyrrols," Akademische Verlag, Leipzig, 1937, Vol. II, Part 1, p. 13.

chloride in dioxan (30 hr. at 20° and 4 hr. at 100°). A solution of the cyano-ketone (0·10 g.) in 85% sulphuric acid (2 c.c.) was kept between 80° and 90° during 1 hr. before being poured on ice. Ethereal extraction of the aqueous mixture afforded the *amide* (IV; X = $CO{\cdot}NH_2$) (0·02 g.), which was sublimed at 220—230°/0·01 mm. in red prisms, m. p. 263—264° (Found: C, 67·8; H, 6·2; N, 14·5. $C_{16}H_{17}O_2N_3$ requires C, 67·8; H, 6·1; N, 14·8%), showing absorption maxima in ethanolic solution at 257, 316, 452 mμ (log ε 4·12, 3·89, 4·53 respectively) and in Nujol or hexachlorobutadiene mulls at 3390 s, 3200 s, 2930 w, 1690 s, 1647 s, 1610, 1600, 1522, 1505, 1450 s, 1373 w, 1337, 1302 s, 1276 s, 1237, 1219 w, 1182, 1063, 1009, 975, 915 w, 865, 797 s, 752 w, 720 w cm.$^{-1}$.

A solution of the cyano-ketone (IV; X = CN) (0·20 g.) in alcohol (300 c.c.) was boiled during 2 hr. with 20% aqueous sodium hydroxide solution (15 c.c.); evolution of ammonia was not detected. On concentration under reduced pressure the solution deposited crude ββ-*di*-(4 : 5-*dimethyl*-2-*pyrrolyl*)*acrylonitrile* (V) (0·18 g.) which recrystallised from ether–*n*-hexane in pale yellow prisms, m. p. 167—168° (Found: C, 74·9; H, 7·1; N, 17·0. $C_{15}H_{17}N_3$ requires C, 75·3; H, 7·2; N, 17·6%), showing absorption maxima in dioxan solution at 355 mμ (log ε 4·50) and in Nujol or hexachlorobutadiene mulls at 3390, 3320 s, 2930, 2190 s, 1547 s, 1500 s, 1470 w, 1289, 1267, 1195, 1155, 1017 w, 970 w, 855 w, 807, 745 cm.$^{-1}$.

Di-(4 : 5-*dimethyl*-2-*pyrrolyl*) *Ketone*.—Prepared according to ref. 17, this compound showed absorption maxima in ethanolic solution at 256, 369 mμ (log ε 3·92, 4·52 respectively) and in Nujol or hexachlorobutadiene mulls at 3200 s broad, 2915, 2860, 2790 w, 1580, 1515 s, 1461, 1390, 1377, 1369, 1345, 1265 s, 1184 s, 1044, 970, 860 s, 827, 805 w, 758, 706 cm.$^{-1}$; these spectra are consistent with a tautomeric hydroxypyrromethene structure. Attempts to condense the compound with either ethyl cyanoacetate or cyanoacetic acid were unsuccessful.

We thank Sir Alexander Todd for his encouragement, the Rockefeller Foundation for generous support, and the Government of India for a Scholarship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 18th,* 1958.]

[17] Fischer and Orth, *Annalen*, 1933, **502**, 251.