ACETYLPORPHYRINS

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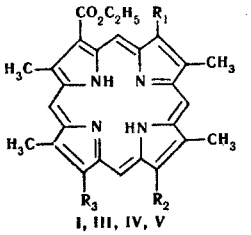
UDC 547.979.733:542.95

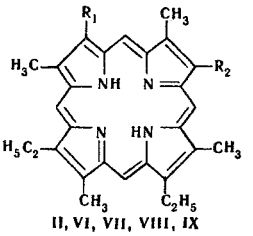
The acetylation of 2-ethoxycarbonyl-1, 4, 5, 8-tetramethylporphyrin and 6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin is examined, and the structure of the monoacetyl derivatives is established. The feasibility of introducing the acetyl group into the meso-position of the porphyrin ring is demonstrated.

In continuation of earlier work on electrophilic substitution reactions of porphyrins with electronegative groups and β-unsubstituted positions [1, 2], we have examined the Friedel-Crafts acetylation of the copper complexes of 2-ethoxycarbonyl-1, 4, 5, 8-tetramethylporphyrin (I) and 6, 8-diethyl-1,3,5,7-tetramethylporphyrin (II), which may be regarded as analogs of deuteroporphyrin-IX.

In alkyl-substituted porphyrins, the unsubstituted β-positions are equivalent towards electrophilic attack, which results in the formation of positional isomers in equivalent amounts, as was shown for the acetylation and formylation of the copper complex of deuteroporphyrin-IX [3]. The introduction of electronegative substitutents into the prophyrin molecule results in a change in the electron density at each unsubstituted β-position. Calculations carried out for I [4] showed some increase in the density at the 3-position adjacent to the ethoxycarbonyl group, in comparison with the equivalent positions 6 and 7. It is therefore suggested that acetylation at the 3-position will be preferred, in the absence of spatial effects.



I, III, IV, V



II, VI, VII, VIII, IX

I $R_1 = R_2 = R_3 = H$; II $R_1 = R_2 = H$; III $R_1 = COCH_3$, $R_2 = R_3 = H$; IV $R_2 = COCH_3$, $R_1 = R_3 = H$; V $R_3 = COCH_3$, $R_2 = R_3 = H$; VI $R_1 = H$, $R_2 = COCH_3$; VII $R_2 = H$, $R_1 = COCH_3$ VIII $R_1 = R_2 = COCH_3$; IX $R_1 = R_2 = H$, meso (α or β) $= COCH_3$

The acetylation was carried out in a mixture of dry chloroform and acetic anhydride, in the presence of stannic chloride, the mixture being held for 10-15 sec at 0°. Under these conditions, the yield of monoacetyl derivatives reached 85-90%, calculated on the reacting complex, and the amount of diacetyl derivatives did not exceed 2-3%.

Separation of the reaction products by preparative thin-layer chromatography on alumina was carried out on the copper complexes, since these are more readily separable by chromatography than the free porphyrins.

Acetylation of the copper complex of 1, 4, 5, 8-tetramethylporphyrin gave prophyrins containing one, two, and three acetyl groups, the electronic spectra of which were completely identical with those prophyrins having the same number of ethoxycarbonyl groups in the same positions [5], but with a bathochromic

Lomonosov Moscow Institute of Fine Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1203-1207, September, 1970. Original article submitted July 11, 1969.

TABLE 1. Physicochemical Properties of Porphyrins and Their Copper Complexes

Compound	Porphyrins			Cu complexes		
	R_f*	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$), chloroform	$\nu_{C=O}$, cm^{-1} acetyl	R_f*	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$), chloroform	$\nu_{C=O}$, cm^{-1} acetyl
II	0,80	398 (184), 498 (14,5), 531,5 (8,55), 567 (6,34), 622 (3,17)		0,91	397 (312), 524 (10,1), 560 (18,4)	
III	0,30	417 (151), 513 (10,2), 551 (6,45), 586 (4,96), 642 (1,49)	1655	0,30	414 (196), 541 (9,8), 584 (12,7)	1657
IV	0,38	412 (137), 515 (6,15), 556 (8,30), 586 (4,80), 643 (1,0)	1655	0,45	411 (161), 541 (6.2), 593 (11,4)	1657
V	0,45	410 (155), 510 (10), 546 (7,2), 583 (5,2), 640 (1,48)	1655	0,52	407 (172), 537 (7,36), 580 (10,4)	1657
VI	0,38	410 (189), 510 (8,88), 549,5 (10,9), 577,5 (6,85), 636 (0,91)	1645	0,49	408 (231), 534 (9,46), 581 (17,18)	1650
VII	0,30	410 (187), 509 (8,63), 549 (10,7), 577 (6,82), 636 (0,91)	1645	0,36	408 (230), 535 (11,6), 581 (18,75)	1650
VIII	0,07	424 (161), 518 (12,6), 553,5 (8,0), 588 (7,0), 642 (3,2)	1646	0,09	421 (164), 544 (12,1), 584 (16,7)	1650
IX	0,39	404 (15), 502 (1), 535,5 (0,5), 573 (0,45), 627 (0,2)	1696	0,63	401 (280), 527,5 (10,2), 563 (14,4)	1700

*The R_f values for II and VI-IX are for the system chloroform – benzene (2:1), on grade IV alumina, and for III-V for chloroform on grade III alumina.

shift of about 1-1.5 nm. Therefore, in establishing the structures of the isomeric acetyl-monoethoxycarbonylporphyrins, we assumed that they must possess spectra similar to those of the isomers of 1, 4, 5, 8-tetramethyl-2(3), (6), (7)-diethoxycarbonylporphyrins.

Comparing the spectra of the compounds obtained by acetylation of I with the corresponding porphyrins [5] having two ethoxycarbonyl groups, and their copper complexes [6], the prophyrin with R_f 0.38 was assigned the structure 2-ethoxycarbonyl-6-acetyl-1, 4, 5, 8-tetramethylporphyrin (IV), on the basis of the "rhodo"-type spectrum of the prophyrin, and the high α/β ratio for the absorption bands of the copper complex. This unequivocally assigns the two electronegative groups to opposite pyrrole rings in the porphyrin molecule. The porphyrin with R_f 0.30 was assigned the structure 2-ethoxycarbonyl-6-acetyl-1, 4, 5, 8-tetramethylporphyrin (III), since the spectrum of its copper complex showed a bathochromic shift of some 4 nm as compared with the other isomer (R_f 0.45), i.e., 2-ethoxycarbonyl-7-acetyl-1, 4, 5, 8-tetramethylporphyrin (V), which is in full agreement with the spectral rules for the copper complexes of 2, 3-diethoxycarbonylporphyrin and 2, 7-diethoxycarbonylporphyrin [6]. These conclusions are supported by the relative amounts of the isomers formed. Thus, IV and V were obtained in the same amounts, whilst III, as predicted by the quantum chemical calculations, was obtained in larger amounts (see Table 1). The bulky ethoxycarbonyl group attached to the pyrrole ring apparently plays little part in the introduction of the acetyl group.

Acetylation of the copper complex of II gave 2- and 4-acetyl derivatives. Assuming that the relative mobilities of both the porphyrins, and their copper complexes, containing acetyl groups in the 2- and 4-positions will be the same as in the related 2- and 4-acetyl derivatives of the dimethyl ester of deuteroporphyrin-IX [3], we assigned to the more mobile isomer the structure 4-acetyl-6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin (VI), and to the less mobile isomer, the structure 2-acetyl-6, 8-diethyl-1,3,5,7-tetraethylporphyrin (VII).

Among the reaction products, in addition to the isomers of the copper complexes VI and VII and a small amount of the copper complex (VIII), we isolated a bright red compound, the mobility of which was intermediate between the copper complexes of II and VI. The IR spectrum of this compound had a strong band at 1700 cm^{-1} (the corresponding porphyrin was of the aetio-type, with a band at 1695 cm^{-1}). It is known [7, 8] that meso-formyloctaalkylporphyrins have aetio-type spectra, with a carbonyl absorption in the 1697 cm^{-1} region, as distinct from the frequency of 1650-1660 cm^{-1} in β-formyl- and β-acetylporphyrins. It has been shown [3] that formylation of deuteroporphyrin-IX affords meso-formylporphyrins, the formyl group entering the α-meso- or the β-meso-position, whichever is the less blocked by the alkyl substituents in the

neighboring pyrrole rings. In comparison with meso-formyloctaalkylporphyrins, the conjugation of the carbonyl group with the prophyrin ring is greatly increased, resulting in a substantial change in the electronic spectrum, and a reduction in the stretching frequency $\nu_{C=O}$ to 1670 cm^{-1}. It is logical to suppose that, in the compound which we isolated, the acetyl group enters in the α-meso- or the β-meso-position, although the interaction of this group with the porphyrin ring is small, being comparable with the effect of the carbonyl group in meso-formyloctaalkylporphyrins. The acetyl group in the meso-position is less stable to concentrated sulfuric acid than that in the β-position.

The introduction of the acetyl group into the meso-position has also been observed in the acetylation of the copper complexes of the dimethyl esters of deuteroporphyrin-IX and III [9].

EXPERIMENTAL

The synthesis of 6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin from 5, 3, 3'-trimethyldipyrrylmethene [10] and 5'-bromo-5-bromomethyl-4, 3'-diethyl-3, 4'-dimethyldipyrrylmethene [11] was carried out by known methods [11].

Copper Complex of 6, 8-Diethyl-1, 3, 5, 7-tetramethylporphyrin. 100 mg of 6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin and 100 mg of copper acetate in 50 ml of chloroform were heated at 60-65° for 30 min. The mixture was cooled, diluted with 100 ml of water, the chloroform layer passed through alumina, the solvent removed, and the complex was crystallized from a mixture of chloroform and methanol. The yield was quantitative, mp 252-253°. Found: C 69.76; H 5.88; N 12.07%. $C_{28}H_{28}CuN_4$. Calculated: C 69.50; H 5.78; N 11.68%.

Acetylation of the Copper Complexes of Prophyrins. A portion of the copper complex (100 mg) of the appropriate porphyrin was dissolved in 50 ml of dry, freshly distilled chloroform, and 10 ml of acetic anhydride was added. The mixture was cooled to 0°, and 0.5 ml of stannic chloride was added with vigorous stirring. Stirring was continued for 10-15 sec, until no further color change to green occurred, then the mixture was poured into water. After neutralization with ammonia, the chloroform layer was separated, dried over sodium sulfate, concentrated to a small volume, and chromatographed on an alumina column with chloroform. Final separation of the copper complexes was effected by preparative thin layer chromatography on grade III-IV alumina with chloroform, followed by recrystallization from a mixture of chloroform and methanol. The free porphyrins were obtained by treating their copper complexes with conc. sulfuric acid for 15 min.

Copper Complex of 2(4)(meso)-Acetyl-6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin. Yield 82%. Found: C 68.82; H 6.16; N 10.27%. $C_{30}H_{30}CuN_4O$. Calculated: C 68.51; H 5.70; N 10.65%.

2(4)(meso)-Acetyl-6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin. Found: C 77.62; H 7.13; N 11.89%. $C_{30}H_{32}N_4O$. Calculated: C 77.60; H 6.90; N 12.09%.

Copper Complex of 2,4-Diacetyl-6,8-diethyl-1, 3, 5, 7-tetramethylporphyrin. Obtained similarly by treatment with acetic anhydride for 5 min. Yield 75%. Mp 286-288°. Found: C 68.05; H 5.80; N 9.99%. $C_{32}H_{32}CuN_4O_2$. Calculated: C 67.67; H 5.63; N 9.86%.

2, 4-Diacetyl-6, 8-diethyl-1, 3, 5, 7-tetramethylporphyrin. Mp above 300°. Found: C 75.54; H 6.71; N 10.57%. $C_{32}H_{34}N_4O_2$. Calculated: C 75.90; H 6.71; N 10.86%.

Copper Complex of 3(6)(7)-Acetyl-2-ethoxycarbonyl-1, 4, 5, 8-tetramethylporphyrin. Yield 87%. Ratio of isomer amounts 2:1:1. Found: C 64.18; H 4.87; N 10.23%. $C_{29}H_{26}CuN_4O_3$. Calculated: C 64.25; H 4.83; N 10.33%.

3(6)(7)-Acetyl-2-ethoxycarbonyl-1, 4, 5, 8-tetramethylporphyrin. Found: C 72.25; H 6.12; N 11.59%. $C_{29}H_{28}N_4O_3$. Calculated: C 72.50; H 5.83; N 11.61%.

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