6. É. R. Zakhs, V. P. Martynova, and L. S. Éfros, Khim. Geterotsikl. Soedin., No. 4, 435 (1979).
7. H. M. van der Bogaert, D. J. Zwaneburg, and T. A. M. M. Maas, Rec. Trav. Chim., 94, 218 (1975).
8. G. C. Levy and G. L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, New York (1972).
9. R. G. Parker and J. D. Roberts, J. Org. Chem., 35, 996 (1970).
10. Yu. M. Chunaev, N. M. Przhiyalgovskaya, L. N. Kurkovskaya, and M. A. Gal'bershtam, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 25, 278 (1982).
11. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. 2, Wiley (1967).

PORPHYRINS.

15.* EFFECT OF STERIC FACTORS ON THE ORIENTATION OF meso SUBSTITUTION IN THE FORMYLATION OF PORPHYRINS. FIRST EXAMPLE OF THE CHROMATOGRAPHIC IDENTIFICATION OF ISOMERS OF PORPHYRINS OF THE I AND II TYPES

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The Cu and Ni complexes of etioporphyrin II were subjected to Vilsmeier formylation, and a steric effect of the peripheral substituents on the direction of electrophilic meso substitution in the porphyrins was observed. The corresponding meso-N,N'-dimethylaminomethyl derivatives, which were separated by thin-layer chromatography (TLC) on silica, gel, were obtained. Their structures were proved by means of the IR, PMR, electronic, and mass spectra.

We have already observed [2] that the chromatographic mobilities of meso-dimethylaminomethylporphyrins depend on the shielding effect of the β-pyrrole substituents adjacent to the meso position. We used this property of meso-dimethylaminomethylporphyrins in the present research to study the influence of steric effects of the substituents in the porphyrin ring on the orientation of meso formylation via the Vilsmeier reaction. Studies of this sort have not been made because of the difficulty or impossibility of separation of isomers of meso-formylporphyrins into individual compounds for the unambiguous interpretation of their structures by physicochemical methods.

As the subject of the investigation we selected etioporphyrin II (I), in which, in the case of monoformylation, electrophilic substitution either in the 5 (15) position between two ethyl groups or in the 10 (20) position between two methyl groups is possible. In order to ascertain the possibility of the effect of the central metal atom on the orientation of meso substitution we carried out the reaction with copper (II) and nickel (III) complexes of porphyrin I. The use of the cobalt complex (IV) led to a mixture of polysubstituted products, and the results of its formylation are therefore not examined in the present paper.

Starting complex II was obtained in 50% yield by cyclization of the corresponding biladiene-a,c dihydrobromide (V) by refluxing in dimethylformamide (DMF) in the presence of copper acetate. After demetallation, complexes III and IV were obtained from porphyrin I by treatment with nickel and cobalt acetates.

The Vilsmeier reaction was carried out by the method that we developed in [3]. Compounds II and III were heated with the Vilsmeier complex ($DMF/POCl_3$) until the starting compounds disappeared completely in the reaction mixtures, while the intermediate "phosphorus complexes" VI and VII were reduced with sodium borohydride in alcohol and the corresponding meso-dimethylaminomethyl (DMAM) derivatives were isolated in 85-91% overall yields.

*See [1] for Communication 14.

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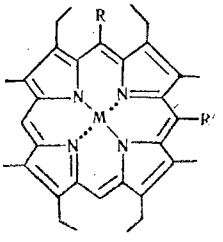
TABLE 1. Physicochemical Properties of the Porphyrins

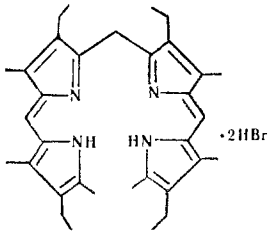
Compound	λ_{max} (chloroform), nm ($\varepsilon \cdot 10^{-3}$)					TLC*
I	399 (165)	502 (11,2)	525 (8,8)	567 (6,1)	620 (4,6)	0,58 (a)
VIIIa	409 (252)	540 (10,5)	578 (12,2)			0,52 (b)
VIIIb	409 (279)	539 (11,3)	577 (13,3)			0,44 (b)
IXa	409 (165)	538 (8,7)	577 (13,3)			0,58 (b)
IXb	408 (165)	536 (8,8)	576 (13,4)			0,51 (b)
Xa	409 (171)	509 (12,1)	545 (7,4)	581 (5,8)	634 (2,7)	0,48 (b)
Xb	408 (171)	508 (12,2)	543 (7,2)	578 (5,5)	630 (2,7)	0,42 (b)
XIIa	411 (163)	512 (10,5)	551 (9,5)	584 (5,9)	639 (4,8)	0,60 (a)
XIIb	410 (155)	510 (9,9)	548,5 (9,0)	582 (5,3)	636 (4,7)	0,60 (a)
XIIIa	410 (175)	549 (7,9)	590 (14,5)			0,79 (a)
XIIIb	409 (187)	544 (8,4)	585 (16,5)			0,79 (a)

*The Rf values are presented for Silufol plates in chloroform (a) and chloroform–ether–alcohol (8.5:1:0.5) (b) systems.

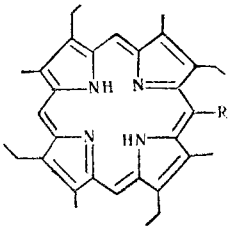
As expected, complexes were formed in each case as a result of the reaction; they were easily separated by means of thin-layer chromatography (TLC) on plates with a fixed layer of silica gel into two isomers (Table 1). We assumed that more mobile VIIIa-Xa isomers contain a DMAM substituent between two ethyl groups, since the ability of the amino meso substituent to react with the acidic surface of silica gel will probably be weaker due to the greater shielding effect of the ethyl groups than when the meso substituent is oriented between two methyl groups in the VIIIb-Xb isomers. The XI isomer [4], which was used as the standard and contains a DMAM group between the methyl and ethyl substituents, had intermediate mobility as compared with the Xa and Xb isomers.



I-IV, VI-X, XII-XIV



V



XI, XV

I M=2H, R=R′=H; II M=Cu, R=R′=H; III M=Ni, R=R′=H; IV M=Co, R=R′=H; VI M=Cu, R(R′)=CH=$\overset{+}{N}$Me$_2$(POCl$_2$)$^-$ (A), R′(R)=H; VII M=Ni, R(R′)=A, R′(R)=H; VIIIa M=Cu, R=CH$_2$NMe$_2$ (B), R′=H; VIIIb M=Cu, R=H, R′=B; IXa M=Ni, R=B, R′=H; IXb R=H, R′=B, M=Ni; Xa M=2H, R=B, R′=H; Xb M=2H, R=H, R′=B; XIIa M=2H, R=B·BH$_3$, R′=H; XIIb M=2H, R=H, R′=B·BH$_3$; XIIIa M=Ni, R=B·BH$_3$, R′=H; XIIIb M=Ni, R=H; R′=B·BH$_3$; XIVa, b M=2H, R(R′)=CHO, R′(R)=H; XI R=B; XV R=B·BH$_3$

Thus the introduction of a DMAM substituent can be used successfully to characterize the isomeric purity of porphyrins of the I and II types and to investigate monopyrrole condensation and other reactions in the synthesis of porphyrins in which the possibility of randomization is not excluded.

The formation of aminoborane complexes XIIa, b and XIIIa, b led to disappearance of chromatographic differences in the isomers. The corresponding meso-formylporphyrins XIVa, b or their oximes also cannot be separated chromatographically into individual isomers.

The structure of the Xa, b isomers obtained by demetallation of the corresponding metal complexes VIIIa and VIIIb were established by PMR spectroscopy. The assumption that in the case of the Xa isomer, which contains a meso substituent between two ethyl groups, the difference in the chemical shifts of the signals of the protons from the two pairs of ring

TABLE 2. PMR Spectra of Porphyrins in $CDCl_3$ (δ Scale)

Compound	meso-H	$-CH_2-N<$	CH_3	CH_2-CH_3	$N-(CH_3)_2$	N—H
I	10,10 s (2H); 10,08 s (2H)		3,64 s (12H)	4,10 q; 1,87 t		−3,77
III	9,77 s (2H); 9,75 s (2H)		3,48 s (12H)	3,92 q; 1,78 t		
IXa	9,31 s (1H); 9,28 s (2H)	5,05 (2H)	3,27 s (6H); 3,24 s (6H)	3,77 q; 1,74 t; 3,72 q; 1,66 t	1,27 s	
IXb	9,33 s (1H); 9,27 s (2H)	5,10 (2H)	3,39 s (6H); 3,29 s (6H)	3,72 q; 1,65 t; 1,55 t	1,33 t	
Xa	10,00 s (2H); 9,83 s (1H)	5,75 (2H)	3,57 s (6H); 3,56 s (6H)	4,01 m; 1,82 m	2,16 s	−2,9
Xb	10,03 s (2H); 9,88 s (1H)	5,87 (2H)	3,66 s (6H); 3,56 s (6H)	4,06 m; 1,85 t; 1,75 t	1,96 s	−2,96
XIIa	10,02 s (2H); 9,89 s (1H)	6,48 (2H)	3,57 s (6H); 3,54 s (6H)	4,02 m; 1,84 t; 1,83 t	1,29 s	−2,76
XIIb	10,02 s (2H); 9,94 s (1H)	6,65 (2H)	3,68 s (6H); 3,56 s (6H)	4,03 m; 1,85 t; 1,73 t	1,35 s	−2,86
XIIIa	9,43 s (1H); 9,40 s (2H)	5,94 (2H)	3,34 s (6H); 3,31 s (6H)	3,86 q; 1,89 t; 3,80 q; 1,74 t	0,91 s	
XIIIb	9,46 s (1H); 9,40 s (2H)	6,13 (2H)	3,52 s (6H); 3,37 s (6H)	3,78 m; 1,73 t; 1,63 t	0,86 s	
XV	10,01 s (1H); 10,00 s (1H); 9,91 s (1H)	6,67 d (1H); 6,46 d (1H); J=15 Hz			1,33 s; 1,30 s	−2,83
XVI	9,47 s (1H); 9,43 s (1H); 9,42 s (1H)	6,09 d (1H); 5,80 d (1H); J=15 Hz			0,86 s; 0,82 s	

methyl groups will be smaller as compared with Xb because of their approximately identical remoteness from the meso substituent served as a basis for the interpretation of the PMR spectra.

In fact, it is apparent from the PMR spectral data (Table 2) that in the spectrum of the mobile Xa isomer the difference in the chemical shifts of the two pairs of methyl ring protons is only 0.01 ppm, as compared with 0.11 ppm in the spectrum of the Xb isomer. A similar pattern can be observed in the PMR spectra of nickel complexes IXa, b in which these differences are 0.03 and 0.10 ppm, respectively, as well as in the spectra of the corresponding aminoborane derivatives XXIa, b and XIIIa, b, which were synthesized by the method in [4].

The formation of aminoborane complexes leads to a fixec conformation of the meso substituent relative to the plane of the porphyrin ring. Their production can therefore be used to unambiguously answer the question as to the identical or different composition of the β-pyrrole groups adjacent to the meso substituent. Thus in the case of etioporphyrin-II the PMR spectra of complexes XIIa, b and XIIIa, b contain singlet signals from the methylene protons of the CH_2-NMe_2 group, whereas splitting of this signal into an AB quartet with J_{AB} = 15 Hz is observed in the case of derivatives of etioporphyrin-I (XV) and coproporphyrin-I (XVI).

It is apparent from Table 1 that the steric hindrance in the Xa isomer, in which the meso substituent is situated between two ethyl groups, leads to great distortion of the porphyrin ring, which is manifested in the bathochromic shift of the electronic spectrum, particularly for the longest-wave band, as compared with the spectrum of the Xb isomer. It is natural that the λ_{max} values in the electronic spectrum of porphyrin XI have intermediate values as compared with the spectra of Xa and Xb [4].

In addition, the ratio of the amounts of isomers in the reaction mixture may serve as a confirmation of their structures. Thus the VIIIa/VIIIb ratio is 1:2 in the formulation of II. Consequently, even small changes in the structure of the β-pyrrole substituents — in this case replacement of the methyl groups by ethyl groups — lead to an appreciable difference in the isomer ratio. Since the electron-density distributions in the meso positions in metal complex II are identical, the differences in the amounts of isomers formed can, upon the whole, be ascribed to the steric effects of the adjacent β substituents. The IXa/IXb ratio in the formylation of III ranges from 1:2 to 1:3. In our opinion, this fact is not associated with the specific effect of the metal on electrophilic substitution but rather with the kinetic peculiarities of the reaction.

We noted that in the process of repeated chromatographic separation the ratio between the isomers changes appreciably (by a factor of several times) to favor an increase in the relative amount of the less mobile isomer because of gradual decomposition of the mobile isomer on the silica gel surface.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in chloroform were recorded with an SF-18 spectrophotometer. The IR spectra of KBr pellets of the compounds were obtained with a Perkin–Elmer model 180 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Bruker WM-250 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-311 spectrometer. Preparative separation of the porphyrin isomers was carried out on 20 by 20 cm plates with a fixed layer of Merck GF-254 silica gel (layer thickness 1 mm) in a chloroform–alcohol system (98:2). The results of thin-layer chromatography (TLC) are presented for Silufol plates.

1,3,7,13,17,19-Hexamethyl-2,8,12,18-tetraethylbiladiene-a,c Dihydrobromide (V). A mixture of 3.4 g (9.0 mmole) of 3,3'-diethyl-4,4'-dimethyl-5,5'-diethoxycarbonyldipyrrolmethane [5], 2.25 g of NaOH, 200 ml of alcohol, and 65 ml of water was refluxed for 4 h, after which the alcohol was removed by distillation in vacuo, and the residue was neutralized to pH 6 with acetic acid. The precipitate was removed by filtration and dried in a desiccator over P_2O_5 to give 5,5'-dicarboxydipyrrylmethane, which was heated at 130°C in vacuo (10.12 mm) for 3 min and cooled. A solution of 2.7 g (18 mmole) of 2,4-dimethyl-3-ethyl-5-formylpyrrole [6] in 36 ml of methanol was added to the cooled residue, the mixture was stirred, and 7.5 ml of 48% HBr solution was added. After 1 h, the precipitate was removed by filtration and air dried to give 4.58 g (77%) of biladiene V. UV spectrum λ_{max} ($\varepsilon \cdot 10^{-3}$): 454 (38.2) and 539 nm (216); in methanol + 1% HBr: 449 (57.1) and 516 nm (69.6). PMR spectrum, ppm: 13.22 (s, 2H, NH), 13.15 (s, 2H, NH), 7.09 (s, 2H, bridged CH), 5.16 (s, 2H, bridged CH_2), 2.69 (s, 6H, Me), 2.29 (s, 6H, Me), 2.22 (s, 6H, Me), 2.53 q – 1.09 t (10H, Et), 2.44 q – 0.62 t (10H, Et). Found: C 60.1; H 7.0; N 8.4%. $C_{33}H_{46}Br_2N_4$. Calculated: C 60.2; H 7.0; N 8.5%.

2,8,12,18-Tetramethyl-3,7,13,17-tetraethyl-21H,23H-porphin (Etioporphyrin-II) (I). A mixture of 1.26 g (1.9 mmole) of biladiene V and 0.9 g (5 mmole) of $Cu(OAc)_2$ was refluxed in a solution of 45 ml of DMF and 15 ml of AcOH for 15 min. After 4 h, the precipitated crystals were removed by filtration and washed with methanol to give 0.52 g (50.4%) of Cu complex II with mp 300°C (from chloroform–methanol). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 397 (307), 524 (11.9), and 561 nm (23.2). Found: N 10.3%. $C_{32}H_{36}CuN_4$. Calculated: N 10.4%. A 0.5-g (0.92 mmole) sample of complex II was dissolved in 10 ml of concentrated H_2SO_4, and the mixture was stirred for 1 h and poured over ice. The aqueous mixture was neutralized to pH 7 with ammonium hydroxide, and the precipitate was separated, dried, and crystallized from chloroform–methanol to give 375 mg (85%) of porphyrin I. Found: C 80.0; H 8.0; N 11.7%. $C_{32}H_{38}Na$. Calculated: C 80.3; H 8.0; N 11.7%.

Nickel Complex of Etioporphyrin-II (III). This compound was obtained in quantitative yield by heating porphyrin I in the presence of $Ni(OAc)_2$ in a solution of chloroform with AcOH. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-23}$): 397 (203), 523 (10.0), and 560 nm (26.8). Found: C 71.8; H 6.8; N 10.6%. $C_{32}H_{36}N_4Ni$. Calculated: C 71.8; H 6.8; N 10.5%.

Cobalt Complex of Etioporphyrin-II (IV). This compound was obtained in 85% yield from porphyrin I by heating in a mixture of chloroform with methanol in the presence of $Co(OAc)_2$. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$) 398 (212), 525 (10.6), and 560 nm (21.2). Found: C 71.6; H 6.8; N 10.5%. $C_{32}H_{36}CoN_4$. Calculated: C 71.8; H 6.8; N 10.5%.

meso-Formyl-2,8,12,18-tetramethyl-3,7,13,17-tetraethyl-21H,23H-porphin (XIVa, b). A mixture of 200 mg (0.37 mmole) of complex II and the complex prepared from 4 ml of DMF and 4.8 ml of $POCl_3$ was refluxed in 100 ml of dry dichloroethane for 20 min, after which the solvent was removed in vacuo, and the residue w heated for 1 h with 100 ml of a saturated solution of sodium acetate. The precipitate was removed by filtration, dried, purified chromatographically with a column filled with aluminum oxide (activity II), and crystallized from chloroform with alcohol to give 197 mg (94%) of the Cu complex of a mixture of isomers of mesoformyletioporphyrin-II. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 402 (220), 530 (10.4), and 567 nm (16.0). Found: N 9.9%. $C_{33}H_{36}CuN_4O$. Calculated: N 9.9%.

Demetallation of the Cu complex in concentrated H_2SO_4 led, after crystallization from chloroform–alcohol, to a mixture of XIVa, b isomers in 86.5% yield. UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 406 (149), 506 (8.3), 539 (6.3), 575 (6.4), and 628 nm (4.2). IR spectrum CO 1695 cm^{-1}. Mass spectrum, m/z (%): 506 (M^+, 40), 478 (100), and 463 (83). Found: C 78.0; H 7.5; N 11.2%. $C_{33}H_{38}N_4O$. Calculated: C 78.2; H 7.6; N 11.1%.

5-Dimethylaminomethyl- (Xa) and 10-Dimethylaminomethyl-2,8,12,18-tetramethyl-3,7,13,17-tetraethyl-21H,23H-porphin (Xb). A 70-mg (0.13 mmole) sample of III and 60 ml of dry dychloroethanewere added to the complex prepared from 1 ml of DMF and 1.2 ml of $POCl_3$, and the mixture was refluxed for 25 min. The solvent was removed in vacuo, the residue was poured into 150 ml of cold water, and the precipitate was removed by filtration and dissolved in a mixture of 30 ml of alcohol and 30 ml of chloroform. Sodium borohydride (100 mg) was added with stirring, and, after 5 min, 150 ml of water was added, and the product was extracted with chloroform. The organic layer was washed with water, dried, and evaporated, and the residue was chromatographed with a column filled with aluminum oxide by elution with chloroform to give 70.2 mg (91%) of a mixture of isomers IXa, b. Found: C 70.8; H 7.2; N 11.7%. $C_{35}H_{43}N_4Ni$. Calculated: C 70.9; H 7.3; N 11.8%. According to the results of TLC on Silufol plates, the isomer ratio was 1:2.5 (by spectrophotometric analysis). Preparative separation of the isomers on plates with silica gel yielded 6.8 mg (10%) of complex IXa and 28 mg (40%) of complex IXb. The following data were obtained for complex IXa. IR spectrum: 2760 and 2810 cm^{-1}. Mass spectrum for $C_{35}H_{43}N_5^{58}Ni$, m/z (%): 591 (M^+, 11), 548 (63), 547 (49), and 546 (100). The following data were obtained for complex IXb. IR spectrum: 2755 and 2810 cm^{-1}. Mass spectrum for $C_{35}H_{43}N_5^{58}Ni$, m/z (%): 591 (M^+, 16), 548 (71), 547 (65), and 546 (100). A 50-mg (0.08 mmole) sample of the mixture of complexes IXa, b was dissolved in 10 ml of concentrated H_2SO_4, and the solution was stirred for 1 h and poured over ice. The aqueous mixture was neutralized to pH 7 with ammonium hydroxide, and the resulting precipitate was removed by filtration, washed with water, dried, and chromatographed with a column filled with aluminum oxide (activity II) by elution with chloroform to give, after crystallization from chloroform–methanol, 38.7 mg (86%) of a mixture of Xa, b isomers. Found: C 78.3; H 8.5; N 13.1%. $C_{35}H_{45}N_5$. Calculated: C 78.5; H 8.5; N 13.1%. Repeated separation by means of preparative TLC on silica gel gave 5.9 mg of porphyrin Xa and 23.4 mg of porphyrin Xb. The following data were obtained for porphyrin Xa. IR spectrum: 2760 and 2810 cm^{-1}. Mass spectrum, m/z (%): 535 (M^+, 19), 492 (93), 491 (65), 490 (100), and 478 (43). The following data were obtained for porphyrin Xb. IR spectrum: 2750 and 2800 cm^{-1}. Mass spectrum, m/z (%): 535 (5), 492 (65), 491 (70), 490 (100), and 478 (13).

Copper Complexes of 5-Dimethylaminomethyl- (VIIIa) and 10-Dimethylaminomethyl-2,8,12,18-tetramethyl-3,7,13,17-tetraethyl-21H,23H-porphin (VIIIb). These complexes were obtained from complex II in an overall yield based on the mixture of isomers of 80–90% by a method similar to that used to prepare complexes IXa, b. According to the results of TLC on Silufol plates, the VIIIa/VIIIb isomer ratio was 1:2. Mass spectrum for the VIIIa isomer ($C_{35}H_{43}{}^{63}CuN_5$), m/z (%): 596 (M^+, 16), 553 (53), and 551 (100). Mass spectrum for the VIIIb isomer ($C_{35}H_{43}{}^{63}CuN_5$), m/z (%): 596 (M^+, 15), 553 (100), and 551 (91).

Borane Complexes of IXa, b and Xa, b and Nickel Complex of meso-Dimethylaminomethylcoproporphyrin-I (XIIIa, b, XIIa, b, and XVI). Typical Method. Diborane was bubbled through a solution of 10 mg of complex IXb in 10 ml of dry THF at 10°C until the starting substance disappeared (according to chromatographic testing), after which the solvent was removed in vacuo, and the residue was chromatographed with a column filled with silica gel (L 40/100, Czechoslovakian SSR) and crystallized from chloroform–alcohol to give 9.6 mg (94%) of complex XIIIb. IR spectrum: 2260, 2310, and 2350 cm^{-1}. Mass spectrum for $C_{35}H_{43}N_5{}^{58}Ni \cdot CH_3$, m/z (%): 605 ($M^+$, 3), 591 (12), 550 (50), 548 (100), and 546 (78). The remaining borane complexes were similarly obtained in 80–90% yields.

LITERATURE CITED

1. G. V. Ponomarev and G. B. Maravin, Khim. Geterotsikl. Soedin., No. 1, 59 (1982).
2. G. V. Kirillova, T. A. Babushkina, V. P. Suboch, and G. V. Ponomarev, Khim. Geterotsikl. Soedin., No. 9, 1215 (1978).
3. G. V. Ponomarev and B.V.Rozynov, Khim. Geterotsikl. Soedin., No. 9, 1172 (1973).
4. G. V. Ponomarev, B. V.Rozynov, T. A. Babushkina, and T. M. Ivanova, Khim. Geterotsikl. Soedin., No. 11, 1518 (1975).
5. H. Fischer and H. Orth, in: Die Chemie des Pyrrols, Leipzig (1934-1940).
6. R. L. N. Harris, A. W. Johnson, and J. T. Kay, J. Chem. Soc. (C), No. 1, 22 (1966).