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Oxidative Dimerization of Pyrrole Derivatives. II. The Formation and Structure of Dimers of 3-Alkoxycarbonyl-substituted Pyrryls[1,2]

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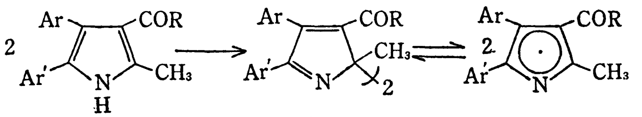
Oxidation of 3-alkoxycarbonyl-substituted pyrrolic compounds with aqueous potassium ferricyanide in the presence of potassium hydroxide afforded 2,2′- and 5,5′-bispyrrolenine derivatives, which were in equilibrium with each other in solution *via* radical intermediates. The substituent effects on the dimer formation will also be discussed in connection with the characters of the intermediate pyrryl radicals.

Several *N*-heteroaromatic compounds have been known to form dimers *via* oxidation, and some of these exist in equilibrium with dissociated radicals.[3a-h] However, the structures of such dimers have not been elucidated except in the case of bis-triarylimidazolyl radicals.[4a,b]

In the previous paper, we reported that some 3-acyl-substituted pyrrole derivatives (I) gave dimers (II) which were in equilibrium with stable pyrryl radicals (III) in solution, on oxidation with potassium ferricyanide.[5a,b]



(I) (II) (III)

The formation of such dimers seems to raise discussion connected with the characters of the radicals, since the intermediacy of the heteroaromatic radicals has been suggested for the oxidative dimerization of *N*-

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[1] Part I of this series: Ref. 5a.

[2] Presented at the 24th Meeting of the Chemical Society of Japan, Tokyo, October, 1971.

[3] a) K. Maeda and T. Hayashi, This Bulletin, **43**, 429, 1431 (1970) and references therein. b) K. Shillfarth and H. Zimmerman, *Chem. Ber.*, **98**, 3124 (1965). c) R. Kuhn and H. Kainer, *Biochim. Biophys. Acta*, **12**, 325 (1953). d) H. Zimmerman, H. Baumgärtel, and F. Bakke, *Angew. Chem.*, **73**, 808 (1961). e) S. M. Blinder, M. L. Peller, N. W. Lord, L. C. Aamodt, and N. S. Ivanchukov, *J. Chem. Phys.*, **36**, 540 (1962). f) Y. Nagai and Y. Sakaino, *Nippon Kagaku Zasshi*, **90**, 309 (1969). g) H. Baumgärtel and H. Zimmerman, *Chem. Ber.*, **99**, 843 (1966). h) H. J. Teuber, G. Schutz, and H. J. Gross, *Angew. Chem.*, **82**, 522 (1970).

[4] a) D. M. White and J. Sonnenberg, *J. Amer. Chem. Soc.*, **88**, 3825 (1966). b) H. Tanino, T, Kondo, K. Okada, and T, Goto, Preprints p. 146, for the 9th NMR Symposium, Kanazawa. August 1970.

[5] a) K. Tomita and N. Yoshida, *Tetrahedron Lett.*, **1971**, 1169. b) K. Tomita and N. Yoshida, Preprints p. 449, for the Third International Congress of Heterocyclic Chemistry, Sendai, August, 1971.

heteroaromatic compounds with potassium ferricyanide.[3a)]

This paper will discuss the formation and structure of the dimers of 3-alkoxycarbonyl-substituted pyrryl radicals obtained from the corresponding pyrrole derivatives. We will also discuss briefly the characters of these radicals on the basis of the substituent effects on the dimer formation.

Results and Discussion

Formation of Dimers. Oxidation of ethyl 4,5-bis(*p*-methoxyphenyl)-2-methylpyrrole-3-carboxylate (IV) with potassium ferricyanide under alkaline conditions afforded a crystalline precipitate (D-IV)[6)] quantitatively. The results of an elemental analysis and the molecular weight of D-IV, listed in Table 1, support the formation of a pyrryl-radical dimer. The reduction of D-IV with hydroquinone affords the pyrrole derivatives IV quantitatively, which shows that the dimer still contains the intact pyrrole ring. The IR spectrum of D-IV is characterized by strong imine absorptions at 1610 cm^{-1} and carbonyl at 1720 cm^{-1} (appearing at 1675 cm^{-1} in IV) and an absence of NH absorptions.

The Occurrence of Equilibrium in D-IV. The NMR spectra of D-IV showed characteristic features, as is shown in Fig. 1.

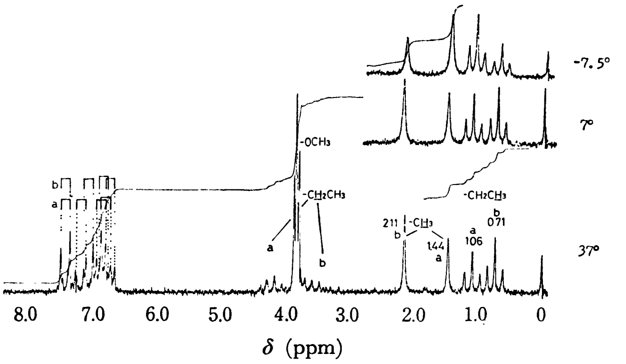
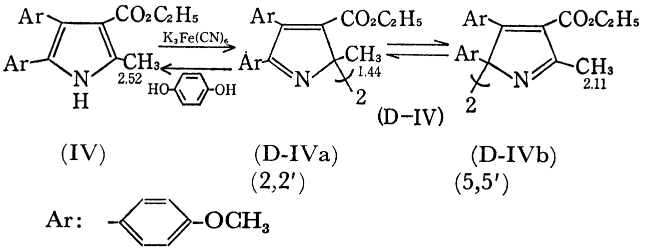


Fig. 1. NMR spectra of D-IV in CDCl$_3$.

Since it shows the presence of the two ester, four *p*-methoxyphenyl, and two methyl groups in a ratio dependent on the temperature, D-IV seems to be a mixture of two dimers, (D-IVa) and (D-IVb) (assigned as *a* and *b* in Fig. 1), which are in equilibrium with each other in solution. In fact, as expected, one of the dimers D-IVa was isolated on the recrystallization of D-IV from acetone.[7)] Its NMR spectrum, measured at −7.5°C immediately after D-IVa was dissolved in cold CDCl$_3$, showed only the signals, *a* in Fig. 1, corresponding to a single compound. With the passage of time, the spectrum showed the gradual appearance of the other isomer, D-IVb, from D-IVa, and after a long time afforded the same pattern of spectrum of a mixture of D-IVa and D-IVb, as is shown in Fig. 1. Those phenomena were also observed on a thin layer chromatogram (tlc); a tlc of D-IV showed two spots (R_f; 0.6 and 0.2, developed in a mixture of benzene and acetone (20 : 1) on a silicagel plate), while that of D-IVa showed one spot (R_f; 0.6) when it was developed immediately, and an additional spot (R_f; 0.2), developed after the solution of D-IVa was allowed to stand for a long time at room temperature.

These results strongly indicate the presence of the equilibrium, though attempt at the isolation and characterization of the other isomer, D-IVb, have thus far been unsuccessful.

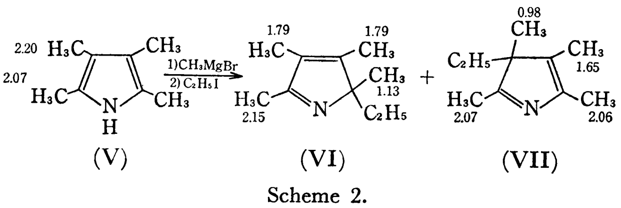
The Structures of D-IVa and D-IVb. The structures of D-IVa and D-IVb were determined to be 2,2′- and 5,5′-bispyrrolenine derivatives respectively, as is shown in Scheme 1, on the basis of the following results.



Scheme 1.

The single 2-methyl signal at 1.44 ppm in the NMR spectrum of D-IVa supported a symmetrical dimer structure, while the two overlapping A$_2$B$_2$-type signals in the aromatic region indicate that the phenyl rings were not involved in the dimerization-bond formation, as they are in the dimer of the triphenylmethyl radical.[8a–d)] The IR spectrum of D-IVa shows the same absorptions as D-IV, and the strong imine absorptions at 1610 cm^{-1} indicate the pyrrolenine structure, eliminating the possibility of the formation of a 1,1′ (N,N′) bond. The absorptions at 1720 cm^{-1} show the presence of an α,β-unsaturated ester group, which also suggests that the formation of a 3,3′ bond is unlikely.

The 2-methyl proton signal in the NMR spectrum of tetramethylpyrrole (V) is markedly shifted upfield with further substitution at the 2-position,[9)] as is shown in Compound (VI) in Scheme 2.



Scheme 2.

In the case of the dimer D-IVa, the methyl signal which appeared at 2.52 ppm in the pyrrolic compound, IV, underwent a remarkable upfield shift to

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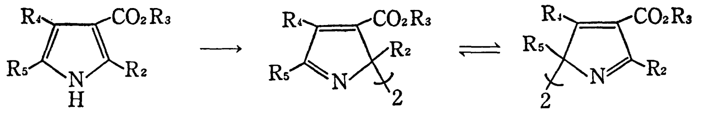
[6)] The dimer of compound (Y) is noted (D-Y) symbolically.

[7)] See Experimental.

[8)] a) H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, **1968**, 249. b) H. A. Staab, H. Brettschneider, and H. Brunner, *Chem. Ber.*, **103**, 1101 (1970). d) R. D. Guthrie and G. R. Weisman, *Chem. Commun.*, **1969**, 1316. d) H. Takeuchi, T. Nagai, and N, Tokura, This Bulletin, **44**, 753 (1971).

[9)] J. L. Wong and M. H. Ritchie, *Chem. Commun.*, **1970**, 142.

TABLE 1.



(IV, VIII—XV) (D-IVa, D-VIIIa—XVa) (2,2′) (D-IVb, D-VIIIb—XVb) (5,5′)

	R_2	R_3	R_4	R_5	Mp °C (decomp.)	IR (CO) (cm^{-1})	NMR 2-CH_3 ($CDCl_3$, 37.0°C) ppm a	b	a : b
D-IV	CH_3	C_2H_5	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	132—135	1725	1.44	2.11	41 : 59
D-IVa					141—143	1725			
D-VIII	CH_3	C_2H_5	CH_3	p-ClC_6H_4	125—128	1715	1.35 2.24$^{a)}$	1.92 2.08$^{a)}$	61 : 39
D-VIIIa					130—133	1715			
D-IX	C_2H_5	C_2H_5	CH_3	p-ClC_6H_4	117—120	1720	2.05$^{b)}$ 2.25$^{a)}$	2.90$^{b)}$ 2.10$^{a)}$	55 : 45
D-IXa					124—126	1720			
D-X	CH_3	CH_3	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	—125$^{c)}$	1730	1.44	2.10	49 : 51
D-XI	CH_3	C_2H_5	C_6H_5	p-$CH_3OC_6H_4$	140—142	1720	1.44	2.15	42 : 58
D-XII	CH_3	C_2H_5	p-$CH_3OC_6H_4$	C_6H_5	130—135	1720	1.46	2.13	50 : 50
D-XIII	CH_3	C_2H_5	C_6H_5	C_6H_5	140—142	1725	1.50	2.15	49 : 51
D-XIIIa					157—159	1725			
D-XIV	CH_3	C_2H_5	p-ClC_6H_4	p-ClC_6H_4	—150$^{c)}$	1720	1.44	2.10	51 : 49
D-XV	CH_3	$CH_2C_6H_5$	CH_3	p-$CH_3OC_6H_4$	125—128	1715	1.30	1.90	58 : 42

	Formula	Anal. Found % C	H	N	Cl	Calcd % C	H	N	Cl	Mass (M+)
D-IV	$C_{44}H_{44}O_8N_2$ (728.81)	72.37	5.97	3.88		72.51	6.09	3.84		728
D-IVa		72.61	6.03	3.97						
D-VIII	$C_{30}H_{30}O_4N_2Cl_2$ (553.47)	65.11	5.48	4.82	12.85	65.10	5.46	5.06	12.81	552
D-IX	$C_{32}H_{34}O_4N_2Cl_2$ (581.56)	66.02	5.94	4.68	12.28	66.08	5.89	4.82	12.19	580
D-IXa		66.05	5.80	4.60	12.21					
D-X	$C_{42}H_{40}O_8N_2$ (700.76)	72.26	5.48	4.02		71.98	5.75	4.00		700
D-XI	$C_{42}H_{40}O_6N_2$ (668.76)	75.15	5.94	4.18		75.43	6.03	4.19		668
D-XII	$C_{42}H_{40}O_6N_2$ (668.76)	75.15	6.05	4.18		75.43	6.03	4.19		668
D-XIII	$C_{40}H_{36}O_4N_2$ (608.70)	78.76	5.95	4.75		78.92	5.96	4.60		608
D-XIIIa		78.88	5.72	4.65						
D-XIV	$C_{40}H_{32}O_4N_2Cl_4$ (746.52)	64.21	4.47	3.67	18.78	64.36	4.32	3.75	19.00	744
D-XV	$C_{42}H_{40}O_6N_2$ (668.76)	74.84	6.08	4.15		75.43	6.03	4.19		668

a) 4-C$\underline{H}_3$. b) 2-C$\underline{H}_2$CH_3. c) obscure.

1.44 ppm. The 2,2′ bond formation was thus assigned for the dimer D-IVa; which was analogous to the dimers II of 3-acylpyrryls III.[5)]

Although the other isomer, D-IVb, was not isolated, its NMR and IR spectra, deduced from a comparison of the spectra of D-IVa with those of the mixture D-IV, also support the symmetrical bispyrrolenine structure in which 1,1′ or 3,3′ bond formation is excluded. In this isomer, the methyl signal (2.11 ppm), which is not shifted upfield as in the case of D-IVa, allows for the possibility of two dimers, 4,4′ or 5,5′, by comparison with the results described by Wong *et al.* (Scheme 2); however the 5,5′ structure, as is shown in Scheme 1, seems reasonable on the basis of the following facts. When the oxidation of the 4-methyl-substituted analogue (VIII) was undertaken, a mixture of two dimers, (D-VIIIa) and (D-VIIIb), also resulted; the isomer isolated on the recrystallization from acetone, D-VIIIa, was identified as a 2,2′-dimer from the same consideration of NMR spectral data, postulated in Scheme 3, as in the case of D-IVa. The 4-methyl proton signal of the other isomer, D-VIIIb, was observed at 2.08 ppm;[10)] this fact strongly supports the 5,5′ structure, since a much larger upfield shift would be expected if the carbon at the 4,4′-position is involved

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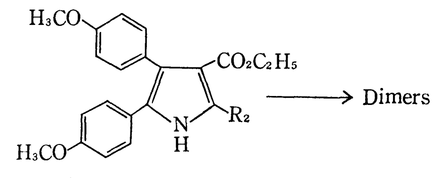
[10)] Assigned on comparison with that of IXb, as shown in Table 1.

TABLE 2.

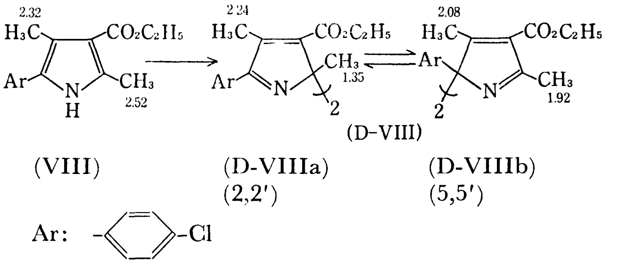


(XVI—XIX) (D-XVI—XVIII)

	R_2	Yield %	Mp °C (decomp.)	IR (CO) cm^{-1}	Formula	Anal. Found % C	Anal. Found % H	Anal. Found % N	Anal. Calcd % C	Anal. Calcd % H	Anal. Calcd % N	Mass (M^+)
D-XVI	C_2H_5	45	130—133	1725	$C_{46}H_{48}O_8N_2$(756.86)	72.84	6.29	3.66	73.00	6.39	3.70	756
D-XVII	i-C_3H_7	10	—65[a]	1725	$C_{48}H_{52}O_8N_2$(784.91)	73.28	7.43	3.77	73.45	6.68	3.57	—[b]
D-XVIII	t-C_4H_9	10	—75[a]	1725	$C_{50}H_{56}O_8N_2$(812.96)	73.06	6.81	3.26	73.87	6.89	3.45	812
D-XIX	H	0(recovery)										
(D-IV	CH_3	quant.										

a) obscure. b) not detected.

in the bonding, as is shown by the 4-methyl proton signal of (VII).



Scheme 3.

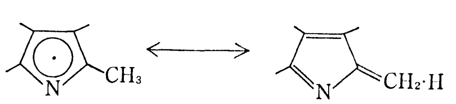
It was found that analogous reactions of some other derivatives (IX—XV) gave the corresponding dimers (D-IX—XV) quantitatively, and that each of them consisted of 2,2′- and 5,5′-bispyrrolenines. Their physical properties, spectral data, and occurrence ratio in equilibrium are summarized in Table 1. It is not clear why the 3-alkoxycarbonyl-substituted derivatives give a mixture of the dimers, while the 3-acyl analogues I afforded only 2,2′ dimers II. It seems, however, that the steric effect of this difference is not important, since the 3-methoxycarbonyl-substituted compound (X) gives two dimers, while the sterically-not-so-un-equivalent 3-propionyl derivative (I, Ar=Ar′=p-$CH_3OC_6H_4$-, R=C_2H_5) forms a single dimer.

The Mechanism of the Interconversion between the 2,2′- and 5,5′-Dimers. We consider that the interconversion of the 2,2′-dimers to 5,5′-isomers proceeds *via* a pyrryl radical as an intermediate, from the reasons described below.

Firstly, the conversion of 2,2′-dimers to 5,5′-dimers is inhibited by hydroquinone. A second reason is based on the substituent effects. Kinetic studies by means of NMR showed that the interconversion obeyed first-order kinetics, and the rate constants, $k_{a\to b}$ and $k_{b\to a}$, for the dimers D-IV and D-XIII were estimated to be 2.7×10^{-3}, 1.9×10^{-3} (D-IV) and 0.75×10^{-3}, 0.71×10^{-3} (D-XIII), both at 37.0°C. Thus, a significant increase in the rate constant was observed for the former; this was explainable from the radical stabilizing ability of the p-methoxy substituent, as was suggested by Zimmerman *et al.*[3g]

The Effect of Substituents on the Dimerization Reactions. In order to estimate the effect of 2-alkyl substituents on the dimerization reactions, Compounds (XVI—XIX) were examined; the results are listed in Table 2.

Table 2 indicates that the 2-alkyl groups have a direct influence on the yield of the dimers. It is likely that the oxidation of these compounds proceeds *via* pyrryl radicals, as was mentioned before; therefore, it seems reasonable to consider that the yield of the dimers depends mainly upon the reactivity of the intermediate pyrryl radicals. As is shown in Table 2, the order of the yields is as follows; $CH_3>C_2H_5>i$-C_3H_7, t-$C_4H_9\gg H$. This order is in accord with that of the stabilizing ability of the radicals by a hyperconjugation effect caused by the 2-alkyl substituents. Thus, in this series, the largest increase in resonance energy can be obtained when R_2 is CH_3 (IV), as is shown below;



On the other hand, in the case of XIX (R_2=H), which gave no dimer, the intermediate pyrryl radical is less stabilized. When R_2 is isopropyl (XVII) and t-butyl (XVIII), however, the remarkable decrease in the yield of the dimers can not be fully explained by a decrease in the hyperconjugation effect. These facts suggest that the dimerization is also markedly subject to steric hindrance by the bulky 2-substituents in the approach of two pyrryl radicals. An analogous steric effect was observed in the case of the acid-catalysed dimerization of 2-alkyl-indole and -benzofuran derivatives.[11,12]

The experimental results, which suggest the effects of substituents at other positions (4 and 5), are shown below.

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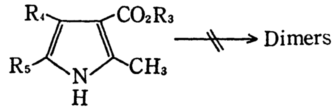
11) G. F. Smith and A. E. Walters, *J. Chem. Soc.*, **1961**, 940.

12) T. Abe and R. Shimizu, *Nippon Kagaku Zasshi*, **91**, 753 (1970).



(XX—XXII)

	R_3	R_4	R_5
XX	$CH_2C_6H_5$	p-$CH_3OC_6H_4$	CH_3
XXI	C_2H_5	H	C_6H_5
XXII	C_2H_5	CH_3	CH_3

These results indicate that the 5-aryl substituent is more essential for the dimer formation than that of the 4-position, since 4-alkyl-5-aryl derivatives (VIII, IX and XV) afford the corresponding dimers in good yields, whereas the 4-aryl-5-alkyl compound (XX) gives no dimer and the starting material is recovered. (However, the effect of the 4-alkyl substituent is not entirely negligible, as is shown by the lack of dimerization of Compound XXI (R_4=H).) From this point of view, the fact that the 4,5-dimethyl-substituted compound (XXII) gives no dimer is very understandable.

Finally, these substituent effects show that the 2- and and 5-substituents play an important role in the stabilization of the pyrryl radicals. Similar substituent effects have been suggested in the case of tetraarylpyrryl radicals.[13a,b)]

The Properties of the Dimers. Some of the dimers, for example, D-IV and D-XI, exhibit thermochromism in solution due to the reversible dissociation of the dimers into pyrryl radicals; this will be shown in detail in the following paper.

Experimental

All the melting points are uncorrected. The IR spectra were determined by means of Nujol mulls with a Hitachi EPI-S2 spectrophotometer; the mass spectra, with a JEOL-JMS-OIS mass spectrometer, and the NMR spectra, with a Varian A-60 NMR spectrometer, using tetramethylsilane as the internal standard.

Materials. The pyrrolic compounds were synthesized by the methods of Davidson[14)] and Knorr[15),16)]

Preparation of D-IV. To a stirred solution of IV (1.0 g) in 100 m*l* of ethanol was added gradually an aqueous solution (100 m*l*) of potassium ferricyanide (1.7 g) and potassium hydroxide (0.3 g) at room temperature. The precipitate which was thus formed was filtered and washed with water repeatedly and then dried at room temperature under reduced pressure. This precipitate of D-IV (0.95 g) was pure enough as to require no further purification. The recrystallization of D-IV from acetone gave D-IVa, while from the other solvents, ethanol or benzene-petroleum ether, a mixture of D-IVa and D-IVb was formed.

The oxidation reactions of other pyrrolic compounds were carried out in a similar way.

The Reaction of D-IV with Hydroquinone. To a solution of D-IV (174 mg) in 20 m*l* of benzene, hydroquinone (50 mg) was added, and then the mixture was heated at 80°C for 15 min under a stream of nitrogen. The solution was placed on an alumina column and eluted with benzene. The residue obtained by the evaporation of the solvent was recrystallized from benzene-petroleum ether, yielding 158 mg of colorless needles, mp 138°C, which were found to be identical with IV on a mixed melting point determination and by a comparison of their IR and UV spectra.

D-XIII and D-XIV also afforded the corresponding pyrrolic compounds, XIII and XIV respectively, both in quantitative yields.

The authors wish to thank Dr. G. Sunagawa, the Director of these Laboratories, and Dr. K. Tanabe for encouragement through the course of this work.

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13) a) B. S. Tanaseichuk, S. L. Vlasova, A. N. Sunin, and V. E. Gavrilov, *Zh. Org. Khim.*, **5**, 144 (1969). b) B. S. Tanaseichuk, S. L. Vlasova, and E. N. Morozov, *ilid.*, **7**, 1264 (1971).

14) D. Davidson, *J. Org. Chem.*, **3**, 361 (1938).

15) L. Knorr and H. Lange, *Chem. Ber.*, **35**, 2998 (1902).

16) N. Yoshida, K. Tomita, K. Wachi, K. Tanaka, and Y. Iizuka, *Yakugaku Zasshi*, submitted.