Notes

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Anodic Acetoxylation of 2-Hydroxy-3-methoxy-5-methylbenzaldehyde and Its Schiff Bases

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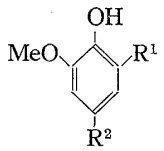
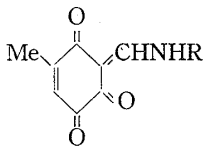
Anodic oxidation of 2-hydroxy-3-methoxy-5-methylbenzaldehyde (II) in acetonitrile–acetic acid (3: 1) containing sodium acetate gave an acetoxylated product in which the acetoxyl group is attached to the side-chain methyl group. On the other hand, oxidation of the Schiff bases (I) derived from II under the same conditions gave cyclohexenetriones. The latter products were shown to be formed by further oxidation of the initially formed acetoxylated Schiff bases, in which the acetoxyl group is introduced into the ring *meta* to the hydroxyl group.

Keywords——anodic acetoxylation; cyclic voltammetry; controlled potential electrolysis; salicylaldehydes; phenolic Schiff bases; cyclohexenetriones

Anodic oxidation of substituted phenols, 2-hydroxy-3-methoxy-5-methylbenzaldehyde Schiff bases (I), in acetonitrile containing an excess of pyridine gave pyridinated phenols in which the pyridinium group is introduced into the ring *meta* to the hydroxyl group.[2)] The result is unusual in comparison with the anodic substitution of a simple phenol, where the substitution takes place exclusively at positions *ortho* or *para* to the hydroxyl group or at a side chain attached to these positions.[3)] An intramolecular participation of the imino group in the molecule of I has been suggested to be responsible for the *meta* substitution.[2)] In order to obtain further suppor[4] for this suggestion, we have examined the anodic acetoxylation of I together with that of the parent aldehyde (II). In the anodic oxidation of 2,6-di-*tert*-butyl-*p*-cresol in acetonitrile–acetic acid (3: 1) containing sodium acetate, acetoxylation has been reported to occur at the position *para* to the hydroxyl group to give 4-acetoxy-2,6-di-*tert*-butyl-4-methylcyclohexa-2,5-dienone as the main product.[4)] Essentially the same solvent system was selected in this study to compare the results with those obtained



Ia: R^1=CH=N-iso-Pr, R^2=Me
Ib: R^1=CH=N-*tert*-Bu, R^2=Me
II: R^1=CHO, R^2=Me
IV: R^1=CHO, R^2=CH_2OAc
V: R^1=CHO, R^2=CHO



IIIa: R=iso-Pr
IIIb: R=*tert*-Bu

Chart 1

1) Location: *133-1 Yamadakami, Suita, Osaka.*
2) *a*) H. Ohmori, A. Matsumoto, and M. Masui, *J.C.S. Chem. Comm.*, **1978**, 407; *b*) *Idem*, *J. Chem. Soc. Perkin II*, **1980**, 347.
3) N.L. Weinberg, "Technique of Electroorganic Synthesis," ed. by N.L. Weinberg, John Wiley and Sons, Inc., New York and London, **1974**, Part I. Chapter IV.
4) A. Ronlan and V.D. Parker, *J. Chem. Soc.* (*C*), **1971**, 3214.

on 2,6-di-*tert*-butyl-*p*-cresol, a typical substituted phenol. The compounds studied and the products obtained (III—V) on controlled potential electrolysis are shown in Chart 1.

Results and Discussion

Figure 1 shows typical voltammograms of Ia and II in acetonitrile–acetic acid (3:1) containing sodium acetate at a glassy carbon electrode. All potentials were measured against an aqueous saturated calomel electrode (S.C.E.). The values of the peak potential (0.65 V) and the peak current (15.8 μA mM^{-1}) for Ia were comparable to those obtained in acetonitrile containing excess pyridine[2b] (0.63 V and 17.8 μA mM^{-1}). The anodic peak at 0.77 V for II must be due to the oxidation of the acetoxylated product (IV) (see below) formed at the first anodic peak, the shoulder at 0.65 V. In the MeCN–pyridine system, II showed anodic peaks at 0.66 and 0.79 V: the latter peak was ascribed to the pyridinated product.[2b]

Table I summarizes the results of exhaustive controlled potential electrolysis of I and II in acetonitrile–acetic acid containing sodium acetate. Details of the procedure and identification of the products are described in the experimental section.

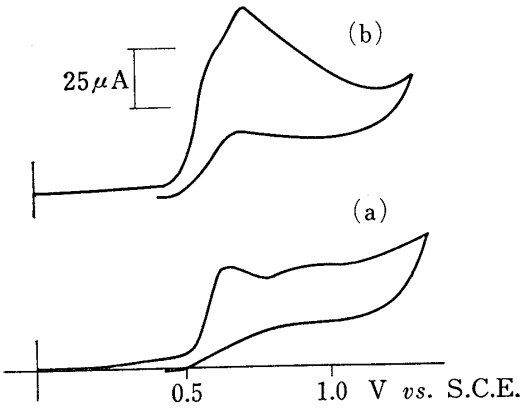


Fig. 1. Cyclic Voltammograms of Ia (2.41 mM) (a) and II (2.23 mM) (b)

In acetonitrile—acetic acid (3:1) containing 0.1 M $NaClO_4$ and 0.25 M NaOAc; glassy carbon anode (area=0.071 cm^2); voltage sweep rate, 0.05 V s^{-1}.

Table I. Results of Exhaustive Controlled Potential Electrolysis[a]

Compound (amount/mmol)	Applied potential (V *vs.* S.C.E.)	*n*-Value	Product isolated (% yield)
Ia (0.39)	0.75	3.9	IIIa (43)
Ib (0.25)	0.75	4.1	IIIb (49)
II (1.02)	0.65	2.0	IV (75)
(1.18)	0.80	3.9	V (52)
IV (0.57)	0.80	2.0	V (73)

a) In acetonitrile-acetic acid (3:1) (50 ml) containing 0.1 M $NaClO_4$ and 0.25 M NaOAc.

Exhaustive electrolysis of I at 0.75 V gave no acetoxylated product, but cyclohexenetriones (III) were isolated after passing 4 F per mol of the substrates (Table I). However, when Ib was electrolyzed at 0.65 V (the voltammetric peak potential of the substrate) and the electrolysis was interrupted after 2 F per mol of the substrate had been passed, a mixture of Ib and the acetoxylated Schiff base (VIIb, R=*tert*-Bu) in a ratio of 1:2 was obtained.[5] Furthermore, constant current electrolysis on Ib gave a similar mixture which contained more than 90% VIIb (see "Experimental"). On exhaustive electrolysis of the latter mixture at 0.75 V, IIIb was formed in 72% yield. These results suggest that the overall oxidation process of I in the controlled potential electrolysis is as shown in Chart 2. Although the exact mechanism of the process VII→III is not known, it seems reasonable that VII is oxidized further at the potential where the starting Schiff base (I) is oxidized.[6] The water

5) When the electrolysis at 0.65 V was continued to completion, an *n*-value of 4 was obtained and IIIb was the main product.

6) Aromatic compounds with an acetoxyl group on the ring are often oxidized more easily than the corresponding compounds without the acetoxyl group: L. Eberson and K. Nyberg, *J. Am. Chem. Soc.*, **88**, 1686 (1966); L. Eberson, *ibid.*, **89**, 4669 (1967); Z. Blum, L. Cedheim, and K. Nyberg, *Acta Chem. Scand. B*, **29**, 715 (1975).

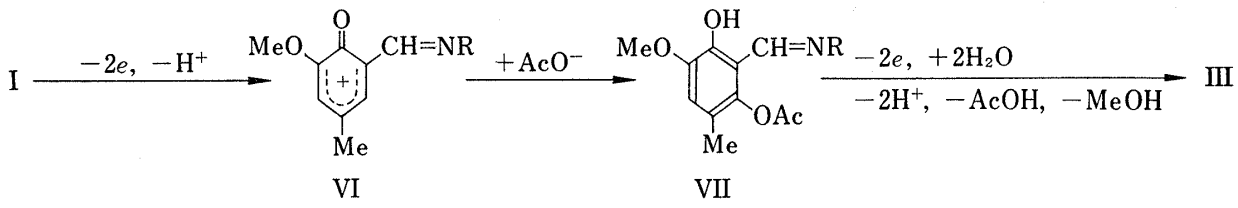


Chart 2

participating in the process is probably water contaminating the medium and/or moisture in the atmosphere. Formation of III from I and VII supports the position of the acetoxyl group in VII.

The side-chain acetoxylated product (IV) obtained on electrolysis of II showed a voltammetric peak at 0.78 V in acetonitrile–acetic acid (3:1) containing sodium acetate, which coincides with the second anodic peak of II under the same conditions (Fig. 1(b)). The results in Table I suggest that the oxidation process of II is as shown in Chart 3. The mechanism of the process II→IV may be similar to that proposed for the side-chain pyridination of II,[2b] where the intermediacy of a quinone methide, 2-formyl-6-methoxy-4-methylene-2,5-cyclohexadien-1-one, has been suggested. The final product (V) showed a voltammetric peak at 0.92 V under the conditions described above.

The PMR spectra of the electrolysis products (III) are summarized in the experimental section. Spin-decoupling experiments revealed coupling between the NH and CH protons in the side chain with $J_{CH,NH}$=15.5 Hz.[7] The value of the coupling constant, which is similar in magnitude to that of H–N–C–H coupling observed for 3-aminoacrylic esters,[8] suggests that the keto-enamine partial structure is a better representation for III than the enol-imine form.[9] The signals due to the methine group in the side chain and the methyl group on the ring observed in various solvents (Fig. 2) suggest that III is a mixture of two isomers with the methyl group *cis* and *trans* to the alkylamino group. Based on the present results alone, however, it is difficult to assign each signal to a particular isomer.

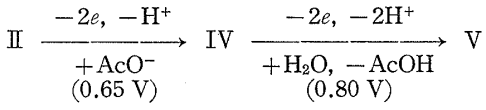


Chart 3

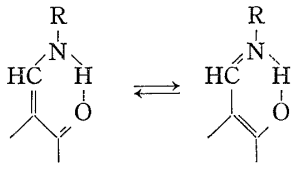


Chart 4

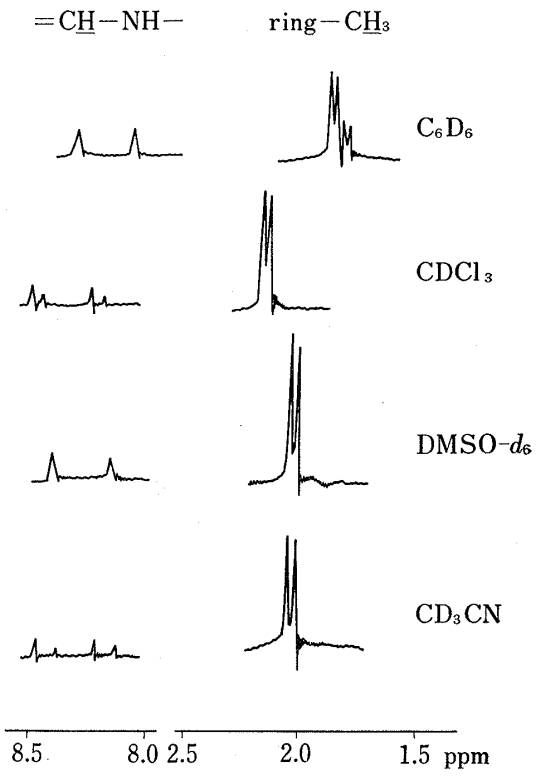


Fig. 2. PMR Signals for the Methine and Methyl Protons of IIIa in Various Solvents

7) J.W. Pavlik and A. van Putten, *Tetrahedron*, **27**, 3301 (1971).
8) W. Bottomley, J.N. Phillips, and J.G. Wilson, *Tetrahedron Lett.*, **1967**, 2957.
9) M.F. Corrigan, I.D. Rae, and B.O. West, *Aust. J. Chem.*, **31**, 587 (1978).

In summary, the intramolecular participation of the imino group in the phenolic Schiff bases (I) is significant in the anodic acetoxylation of the compounds.

Experimental

Materials——2-Hydroxy-3-methoxy-5-methylbenzaldehyde (II) and its Schiff bases (I) were the same material as in previous studies.[2] Sodium perchlorate[10] and acetonitrile[2b] were purified as described previously. Other chemicals were of reagent grade and were used without further purification.

Apparatus——Cyclic voltammetry,[11] controlled potential electrolysis,[11] and constant current electrolysis[2b] were carried out essentially as described previously. All voltammetric measurements were carried out at $25 \pm 0.1°$. IR and PMR spectra were obtained using Hitachi EPI-2 and R-22 spectrometers, respectively.

Controlled Potential Electrolysis——Typical examples of the procedure are described below. A glassy carbon plate anode was used throughout. All electrolyses were carried out in acetonitrile–acetic acid (3: 1, v/v; 50 ml) containing 0.1 M $NaClO_4$ and 0.25 M NaOAc.

a) The phenolic Schiff base (Ia) (80.8 mg) was subjected to electrolysis at 0.75 V at room temperature until the value of the current fell below 5% of the initial value. From the current-time curve, 147 C, which corresponded to $n=3.9$, was found to have been consumed. The anolyte was concentrated to one-tenth of its original volume under reduced pressure, and then diluted with water (50 ml). The resulting mixture was extracted with chloroform (2×50 ml), and the extract was washed and dried. The chloroform was removed under reduced pressure and the residue was subjected to column chromatography on silica gel with chloroform–*n*-hexane (10: 1). The yellow needles obtained (34.7 mg, 43%) from the first effluent were identified as 3-(N-isopropylaminomethylene)-5-methyl-5-cyclohexene-1,2,4-trione (IIIa); mp 133°. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.75; H, 6.34; N, 6.65. IR ν_{max}^{Nujol} cm^{-1}: 3590, 3200, 1681. PMR ($CDCl_3$) δ:[12] 1.44 (6H, doublet, $J=6.5$ Hz, $CH(C\underline{H}_3)_2$), 2.13 (3H, doublet, $J=1.5$ Hz, ring-$C\underline{H}_3$), 3.87 (1H, septet, $J=6.5$ Hz, $C\underline{H}Me_2$), 6.69 (1H, multiplet, ring-$\underline{H}$), 8.30 and 8.34 (1H, two doublets, $J=15.5$ Hz, =C$\underline{H}$–NH–) (see "Results and Discussion"), 11.78 (1H, broad signal,[13] N$\underline{H}$).

3-(N-*tert*-Butylaminomethylene)-5-methyl-5-cyclohexene-1,2,4-trione (IIIb) was obtained similarly as yellow needles (26.6 mg from 54.6 mg of Ib, 49%); mp 121°. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.84; N, 6.26. MS *m/e*: 221 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1681, 1659. PMR ($CDCl_3$) δ:[12] 1.49 (9H, singlet, $C(C\underline{H}_3)_3$), 2.12 (3H, doublet, $J=1.5$ Hz, ring-$C\underline{H}_3$), 6.67 (1H, multiplet, ring-$\underline{H}$), 8.30 and 8.35 (1H, two doublets, $J=15.5$ Hz, =C$\underline{H}$–NH–) (see "Results and Discussion"), 11.70 (1H, broad signal,[13] N$\underline{H}$).

b) Ib (171.6 mg) was subjected to electrolysis at 0.65 V. The electrolysis was discontinued when 150 C, which corresponded to $n=2.0$, had been consumed. After working up the anolyte by essentially the same procedure as in a) except for the chromatographic separation, the crude product was subjected to vacuum distillation (130°, 1 mmHg) to give an orange oil (171 mg). The PMR spectrum of the product suggested that the oil was a mixture of Ib and the acetoxylated Schiff base (VIIb) in a ratio of 1: 2 (see below).

c) II (170 mg) was subjected to electrolysis at 0.65 V until the value of the current fell below 1% of the initial value. After working up the anolyte by essentially the same procedure as in a), except for the chromatographic separation, the crude product was recrystallized from *n*-hexane to give colorless needles, which were identified as 3-formyl-4-hydroxy-5-methoxybenzyl acetate (IV) (170 mg, 75%); mp 98°. *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.85; H, 5.37. Found: C, 58.92; H, 5.40. MS *m/e*: 224 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3213, 1736, 1660. PMR ($CDCl_3$) δ:[12] 2.09 (3H, singlet, $COC\underline{H}_3$), 3.91 (3H, singlet, Ar–$OC\underline{H}_3$), 5.04 (2H, singlet, Ar–$C\underline{H}_2$–), 7.09 (1H, doublet, $J=2$ Hz, Ar$\underline{H}$), 7.70 (1H, doublet, $J=2$ Hz, Ar$\underline{H}$), 9.89 (1H, singlet, ArC$\underline{H}$O), 10.08 (1H, singlet, ArO$\underline{H}$). Electrolysis of II (197 mg) at 0.80 V followed by similar work-up gave 4-hydroxy-5-methoxybenzene-1,3-dicarbaldehyde (V) (111 mg, 52%) as yellow needles; mp 120°. The IR and PMR spectra and the melting point of the product coincided with those of an authentic sample prepared by the reported method.[14]

Constant Current Electrolysis of Ib——Ib (353.7 mg) was subjected to electrolysis in the medium employed for the controlled potential electrolyses at an electrolytic current of 50 mA s^{-1}. A beaker (50 ml) was used as the electrolysis cell, and a piece of reticulated glassy carbon (RVC Products Co. Ltd. RVC 2×1-45-s; 8.38 cm^3; area *ca.* 226 cm^2) and a platinum foil were used as the anode and the cathode, respectively. The electrolysis was continued until 400 C, which corresponded to $n=2.7$, had been consumed. The electrolyzed

10) M. Masui and H. Ohmori, *J. Chem. Soc. Perkin II*, **1972**, 1882.
11) H. Sayo and M. Masui, *J. Chem. Soc. Perkin II*, **1973**, 1940; H. Ohmori, S. Nakai, and M. Masui, *J. Chem. Soc. Perkin I*, **1978**, 1333.
12) $SiMe_4$ was used as an internal standard.
13) Probably a doublet or doublet of doublets through coupling with the methine proton (see "Results and Discussion").
14) E. Profft and W. Krause, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **298**, 148 (1965).

solution was worked up as described above (see b) in the preceding section). The orange oil obtained (357 mg) consisted mainly of the acetoxylated Schiff base (VIIb). IR ν_{max}^{Nujol} cm^{-1}: 2950, 1770, 1633, 1475, 1275, 1200. PMR ($CDCl_3$) δ:[12] 1.35 (9H, singlet, $C(CH_3)_2$), 2.04 (3H, singlet, $COCH_3$), 2.32 (3H, singlet, $Ar-CH_3$), 3.82 (3H, singlet, $Ar-OCH_3$), 6.62 (1H, singlet, ArH), 8.19 (1H, singlet, Ar–CH=N–); the signal for the proton of the hydroxyl group was not discernible.

The product obtained above (250.5 mg) was subjected to controlled potential electrolysis at 0.75 V until the value of the current fell below 1% of the initial value. From the current-time curve 144 C, which corresponded to $n=1.7$, was found to have been consumed. Work-up of the anolyte as described above (see a) in the preceding section) gave IIIb in 72% yield (142.7 mg).

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Facile Preparation of 5-(3-Indolylmethylene)hydantoins

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A facile preparation of 5-(3-indolylmethylene)hydantoins, which are useful intermediates for syntheses of tryptophan and its derivatives, was achieved by condensation of hydantoin with 3-(aminomethylene)-3H-indoles formed *in situ* by the reaction of indoles with Vilsmeier-Haack reagent followed by neutralization with anhydrous bases.

Keywords——tryptophan; hydantoin; 5-(3-indolylmethylene)hydantoin; 3-(aminomethylene)-3H-indole; Vilsmeier-Haack reaction; condensation

It is desirable to develop a convenient synthetic method for tryptophan, an essential amino acid, and its derivatives, some of which are of interest as nonnutritive sweeteners[2] or are components of interesting bioactive peptides.[3] The synthesis of 5-(3-indolylmethylene)-hydantoin (**5a**) which is a useful intermediate for the preparation of tryptophan,[4] has been conventionally performed through two steps *via* indolecarbaldehyde (**4a**): the formylation of indole (**1a**) and subsequent condensation with hydantoin in a secondary amine (route A in the Chart).[4a,5] In the preceding paper, we reported[6] that 3-(aminomethylene)-3H-indole (**3**) is reactive towards active methylene compounds, affording condensation products in good yields. Concerning **3**, Smith reported[7] that 3-(dimethylaminomethylene)-3H-indole was formed as an unstable intermediate in the synthesis of **4a** by neutralization of the iminium salt (**2**) which was generated by the reaction of **1a** with Vilsmeier-Haack reagent. These results suggest that Smith's intermediate (**3**) might be available for the preparation of

1) Location: *16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.*
2) *a*) E.C. Kornfeld, J.M. Sheneman, and T. Suarez, Ger. 1917844 (Nov. 6. 1969): *Chem. Abstr.*, **72**, 30438*c* (1970); *b*) *Idem*, Japan 73-16624 (Apr. 23. 1973); *c*) S. Yamada, M. Yamamoto, C. Hongo, and I. Chibata, *J. Agr. Food. Chem.*, **23**, 653 (1975).
3) *a*) T. Shiba, Y. Mukunoki, and H. Akiyama, *Tetrahedron Lett.*, **1974**, 3085; *b*) B. Angeliki, A. Renate, and T. Wieland, *Justus Libigs Ann. Chem.*, **1974**, 1580, and references therein.
4) *a*) W.J. Boyd and W. Robson, *Biochem. J.*, **29**, 2256 (1935); *b*) E.C. Britton and J.E. Livak, U.S. 2435125 (Jan. 27, 1948): *Chem. Abstr.*, **42**, 4613b (1948); *c*) J. Elks, D.F. Elliott, and B.A. Hems, *J. Chem. Soc.*, **1944**, 629; *d*) R.H. Marchant and D.G. Harvey, *ibid.*, **1951**, 1808.
5) *a*) A.C. Shabica, E.E. Howe, J.B. Ziegler, and M. Tishler, *J. Amer. Chem. Soc.*, **68**, 1156 (1946); *b*) J.E. Livak and M.F. Murray, U.S. 2435399 (Fev. 3. 1948): *Chem. Abstr.*, **42**, 4613*b* (1948).
6) T. Moriya, K. Hagio, and N. Yoneda, *Chem. Pharm. Bull.*, **28**, 1711 (1980).
7) G.F. Smith, *J. Chem. Soc.*, **1954**, 3842.