ELECTROCHEMICAL OXIDATION OF METHYLINDOLES

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Electrochemical oxidation of 1-methylindole (*I*), 1,3-dimethylindole (*II*) and 1,2-dimethylindole (*III*) on a platinum anode in methanol, containing ammonium bromide, was studied. A more profound oxidation as compared with benzofuran or benzothiophene derivatives is indicated by the obtained products: 1-methyl-2,2-bis(1-methylindol-3-yl)-3-indolinone (*IV*), 1,1′-dimethyl-$\Delta^{3,3}$-biindolin-2,2′-dione (*V*), 3,3-dibromo-1-methyl-2-indolinone (*VI*), 3,3,5-tribromo-1-methyl-2-indolinone (*VII*), 3-bromo-1-methyl-2,3-indoledione (*VIII*), 3-methoxy-1,3-dimethyl-2-indolinone (*IX*), 3-hydroxy-1,3-dimethyl-2-indolinone (*X*), 3,5-dibromo-1,3-dimethyl-2-indolinone (*XI*) and 3-bromo-1,2-dimethylindole (*XII*). The ratio of the products can be significantly influenced by the electrolysis conditions. The oxidation takes place in positions 2 and 3 of the indole molecule, the position 2 influencing decisively the oxidation path.

In connection with the extension of our electrochemical oxidation studies on furan and thiophene derivatives to pyrrole derivatives, some simple indole derivatives were oxidized in order to compare the results with the known course of preparative electrolyses of benzofuran and benzothiophene compounds. The oxidation of benzofuran derivatives is similar to the Clauson–Kaas reaction in the furan series, taking place in this case at positions 2 and 3 of the benzofuran nucleus, Electrochemical oxidation in methanol using various auxiliary electrolytes (H_2SO_4, $NaClO_4$, KOH) affords 2,3-dialkoxy-2,3-dihydro derivatives in good yields[1]. Analogous oxidations of benzothiophenes gave, in addition to extensive polymerization and the expected dialkoxydihydro derivative, also substitution products with one or more methoxy groups[2]. This difference, which can be explained by a more even distribution of electrons in the benzothiophene system, is more pronounced in these benzo derivatives than in the parent furan or thiophene systems[3]. We have now extended these studies to benzo derivatives of pyrrole, *i.e.* to indole compounds. Electrochemical oxidation of pyrrole nucleus is to a certain extent similar to that of a furan or thiophene ring. It is assumed that the first step is the same two-electron oxidation, however, the product is better oxidizable, so that the overall six-electron oxidation process affords 2,2,5,5-tetramethoxy-2,5-dihydro derivative[4,5].

In order to be able to compare preparative electrolyses of the indole compounds with those of the benzofuran or benzothiophene compounds, we performed our

studies under essentially the same conditions (electrolysis at constant current, methanolic medium, platinum anode and nickel cathode), however, the specific character of the nitrogen heterocycle required some changes in the electrolysis procedure. Preliminary experiments with indole have shown (in accord with the pyrrole series[5]) that the indole substrate must be substituted at the nitrogen atom in order to obtain other products than resins. Therefore, 1-methylindole (*I*) was chosen as the parent compound investigated. Because of instability of indole substrates in acidic media it was not possible to use acid electrolytes such as H_2SO_4; however, even experiments with other electrolytes ($NaClO_4$, CH_3ONa, KOH) did not afford at least relatively stable identifiable products. The best electrolyte proved to be ammonium bromide (used in the classical Clauson–Kaas reaction). With this electrolyte the indole substrates underwent not only brominations, known with thiophene substrates[6] and observed also in the pyrrole series[7], but mainly complex oxidations which will be discussed further.

The electrolyses of indole substrates were carried out in 10 mmol batches. After electrolysis for the time corresponding to the passage of the required amount of electricity at the chosen anode current density, the reaction solution was worked up and the organic portion was separated by column chromatography. The separated components were identified by spectral data and elemental analyses. The results of the electrolyses are summarized in Table I.

Anodic oxidation of 1-methylindole (*I*) afforded usually mixture of products containing also the unreacted compound. The composition of the reaction mixture was markedly influenced by the total amount of electricity and anode current density. Following compounds were identified among the products: 1-methyl-2,2-bis(1-

TABLE I
Electrolyses of methylindoles

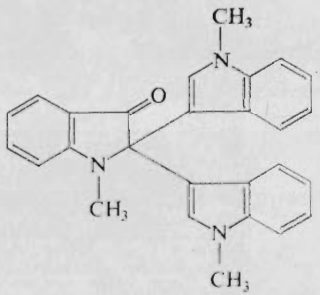
Starting compound	Amount of electricity, F mol^{-1}	Current density (anode), mA cm^{-2}	Identified products %[a]
I	2	20	*I* (34%), *IV* (53%)
I	4	20	*I* (23%), *IV* (14%), *V* (28%), *VI* (8%)
I	4	40	*I* (19%), *IV* (33%), *V* (15%), *VI* (13%)
I	8	40	*VI* (13%), *VII* (22%), *VIII* (6%)
II	4	40	*IX* (70%), *X* (12%), *XI* (5%)
III	4	40	*XII* (42%)

[a] The yield of the isolated component is given as the corresponding stoechiometric portion of the substrate.

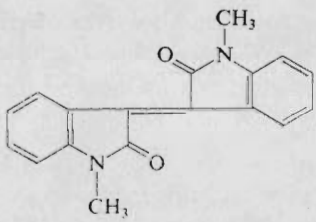
-methylindol-3-yl)-3-indolinone (*IV*), 1,1'-dimethyl-$\Delta^{3,3'}$-biindoline-2,2'-dione (*V*) 3,3-dibromo-1-methyl-2-indolinone (*VI*), 3,3,5-tribromo-1-methyl-2-indolinone (*VII*) and 5-bromo-1-methyl-2,3-indoledione (*VIII*).

Comparison of the experiments shows that the trimeric and dimeric non-brominated products *IV* and *V* prevail when a lower amount of electricity (2–4 F . mol^{-1}) is used. If the amount is increased to 8 $Fmol^{-1}$, 1-methylindole reacts completely, giving rise, however, to a substantial amount of resinous compounds in addition to the brominated oxidation products (the yield of the identified products is only 41%).

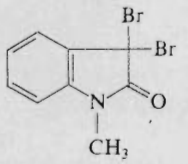
In spite of large structural variety of products of oxidation of 1-methylindole (*I*), the oxidative attack at the positions 2 and 3 is obvious. In order to decide which position plays a more important role, we studied 1,3-dimethylindole (*III*). The anodic oxidation of 1,3-dimethylindole had a more unequivocal course. All the products, indetified in this reaction (compounds *IX*–*XI*) are oxindole derivatives: 3-methoxy-1,3-dimethyl-2-indolinone (*IX*), 3-hydroxy-1,3-dimethyl-2-indolinone (*X*) and 3,5-



IV



V



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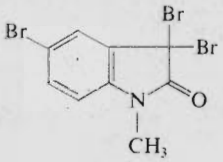
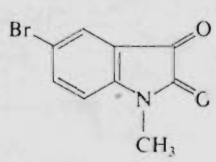
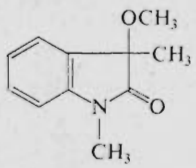


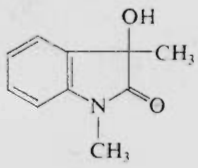
VII



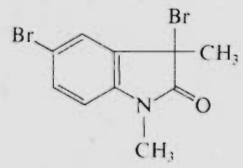
VIII



IX



X



XI

-dibromo-1,3-dimethyl-2-indolinone (*XI*). In addition to these compounds, of which the compound *IX* is the main product, other bromo derivatives of unknown structure were formed in minor amounts. On the other hand, the electrolysis of 1,2-dimethylindole afforded, besides decomposition products, a compound of different character: an unstable bromination product – 3-bromo-1,2-dimethylindole (*XII*).

The structure of the products *IV*–*VIII* is so different that their formation cannot be expressed by a common mechanism. We can visualize already two competing primary electrochemical processes. Besides the one-electron oxidation, affording the indole radical-cation (which undergoes a subsequent chemical or electrochemical reaction), bromonium cation, generated from the electrolyte ions, can form with the indole derivative also a reactive intermediate. In addition to further losses of electrons, the nucleophilic character of the medium (methanol) plays a significant role in the formation of the final structure. The results of our electrochemical oxidations do not indicate that electrochemically generated elemental bromine is responsible for the formation of the compounds isolated. Only some of the brominated products can be correlated with the results of special bromination procedures (N-bromosuccinimide in tert-butyl alcohol[8]). On the other hand, the non-brominated trimeric product has its analogy in products of oxidation of indole compounds with selenium dioxide[9], hydrogen peroxide[10] or photochemically[11].

Similarly to other benzo derivatives of five-membered heterocycles with one hetero atom, the indole derivatives are oxidatively attacked at the heterocyclic nucleus (in positions 2 and 3). In the case of indole substrates, a deeper oxidation takes place under formation of oxo derivatives. Comparison of results of anodic oxidations of substrates *II* and *III* shows that the position 2 of the indole nucleus is important for the oxidation process, leading to the transformation of the original "enamine", grouping into an "imide" bond in the oxindole derivatives.

EXPERIMENTAL

The melting and boiling points are uncorrected. Solid analytical samples were dried for 24 h at 7 Pa. The ^{1}H-NMR spectra were taken on a Varian XL 100 (100 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard, IR spectra were measured on a Perkin Elmer 325 spectrophotometer in tetrachloromethane or (under 1 000 cm^{-1}) in carbon disulfide. Mass spectra were taken on a Gas Chromatograph-Mass Spectrometer LKB 9 000 instrument. Column chromatography was performed on Silpearl silica gel (Kavalier, Czechoslovakia), analytical thin-layer chromatography on Silufol UV 254 sheets (binder starch; Kavalier, Czechoslovakia) or on plates with 5% $CaSO_4$ as binder (Kieselgel G, Merck).

Preparation of Substrates

1-*Methylindole* (I) was prepared according to ref.[12].

1,3-*Dimethylindole* (II): A mixture of 1-methyl-3-indolecarbaldehyde (0·1 mol), diethylene glycol (100 ml), 80% hydrazine hydrate (about 0·3 mol) and potassium hydroxide (22·5 g; 0·4 mol)

was heated till the nitrogen evolution started. After the vigorous reaction had subsided, the mixture was heated to 180°C for 2 h. After cooling and addition of water (200 ml), the organic layer was taken up in chloroform (4 × 50 ml), the solution dried over magnesium sulfate and taken down. Distillation of the residue *in vacuo* afforded 9·0 g (62%) of 1,3-dimethylindole, b.p. 150°C/2·27 kPa; stated[13] b.p. 103—105°C/267 Pa.

1-*Methyl*-3-*indolecarbaldehyde* (according to preparation of 3-indolecarbaldehyde[14]): Phosphorus oxychloride (43 ml, 72 g; 0·47 mol) was added dropwise under stirring and cooling (ice-bath) to dimethylformamide (150 ml). A solution of 1-methylindole (56·5 g; 0·43 mol) in dimethylformamide (50 ml) was then added at a temperature below 10°C. The mixture was stirred at 35°C for 1·5 h, a solution of sodium hydroxide (190 g) in water (500 ml) was added and the temperature raised to the boil. The product which crystallized on standing in a refrigerator was washed with water. Crystallization from ethanol afforded 62 g (90%) of the formyl derivative, m.p. 66—67°C (ref.[15] states 68—69°C).

1,2-*Dimethylindole* (III) was prepared according to the published procedure[16], instead of methyl *p*-toluenesulfonate the methylation was carried out with dimethyl sulfate with the same result.

Electrolyses

The all-glass electrolyser contained two coaxial cylindrical electrodes (a platinum 25 cm^2 anode and a nickel cathode), the cathode space being separated by sintered glass. The electrolyser was equipped with a magnetic stirrer in the anode space, a neck for thermometer and for taking samples. The anode and cathode spaces were closed with calcium chloride tubes. External cooling was applied. The electrolyser was filled with a solution of ammonium bromide (9·8 g) in methanol (200 ml) (concentration 0·5 mol l^{-1}) and the indole substrate (10 mmol) was placed into the anode space. The electrolysis was performed with constant current 0·5—1 A (according to the current density chosen) at 10—30 V for the time required for the passage of the required amount of electricity. The temperature was maintained at —10 to 0°C by means of an ethanol–solid CO_2 bath. After the end of the electrolysis, most of the methanol was evaporated, the residue was mixed with water and extracted with ether or chloroform. After drying over magnesium sulfate the solvent was evaporated and the residue separated by column chromatography (silica gel; gradient elution with benzene–methanol).

Compounds Obtained by Electrolysis

The electrolysis mixtures (for the content of identified components see Table I) were separated by the above-described procedure and the products were characterized by their elemental analyses and NMR, IR and mass spectroscopy. Data for the already known compounds agreed with those published.

1-*Methyl*-2,2-*bis*(1-*methylindol*-3-*yl*)-3-*indolinone* (IV): m.p. 220—222°C, ref.[9] 214—216°C. ^{1}H-NMR spectrum (δ in ppm): 3·32 (s, 3 H, N′-CH_3), 3·66 (s, 6 H, N—CH_3), 6·8—7·5 (m, 14 H arom.). IR-spectrum (cm^{-1}): 742 s, 752 m, 912 w, 1 013 w, 1 085 w, 1 122 w, 1 145 w, 1 248 w, 1 328 m, 1 372 m, 1 421 w, 1 480 s, 1 490 m, 1 611 s, 1 726,s, 2 930 m, 3 060 w. Mass spectrum (*m*/*z*, rel. intensity, %): 405 (33), 404 (100), 377 (28), 376 (83), 292 (30), 291 (70), 275 (25), 248 (20), 247 (63), 81 (14), 69 (17), 67 (13), 57 (23), 55 (23), 45 (30), 43 (25), 41 (22).

1,1′-*Dimethyl*-$\Delta^{3,3'}$-*biindoline*-2,2′-*dione* (V): m.p. 275°C, ref.[17] 275—275·5°C. ^{1}H-NMR spectrum (δ in ppm): 6·28 (s, 6 H, CH_3), 6·65—7·45 (m, 8 H arom.). IR-spectrum (cm^{-1}): 869 w, 936 w, 1 029 w, 1 078 w, 1 095 s, 1 139 m, 1 160 w, 1 268 w, 1 310 w, 1 340 m, 1 350 m,

1 376 s, 1 424 w, 1 475 s, 1 488 m, 1 580 w, 1 615 s, 1 598 s, 2 920 w, 3 000 w. Mass spectrum (*m/z*, rel. intensity, %): 291 (24), 290 (100), 262 (45), 261 (14), 233 (24), 219 (13), 218 (15), 145 (14), 117 (12), 57 (12), 43 (12), 36 (16), 28 (80).

3,3-*Dibromo*-1-*methyl*-2-*indolinone* (VI): m.p. 202—204°C; ref.[17] 200—203°C. ^{1}H-NMR spectrum (δ in ppm): 3·26 (s, 3 H, CH_3), 6·7—7·6 (m, 4 H arom.). IR-spectrum (cm^{-1}): 809 w, 906 m, 937 w, 1 017 w, 1 090 s, 1 128 m, 1 154 w, 1 254 w, 1 342 m, 1 375 m, 1 472 s, 1 490 m, 1 613 s, 1 719 m, 1 746 s, 2 950 w, 3 010 w. Mass spectrum (*m/z*, rel. intensity, %): 305 (13), 304 (26), 303 (13), 226 (100), 225 (31), 224(100), 198 (17), 196 (17), 146 (22), 117 (37), 116 (29), 102 (24), 90 (29), 89 (36), 76 (26), 75 (28).

3,3,5-*Tribromo*-1-*methyl*-2-*indolinone* (VII): m.p. 150—152°C. For $C_9H_6Br_3NO$ (383·9) calculated: 28·16% C, 1 58% H, 3·65% N, 62·45% Br; found: 28·28% C, 1·59% H, 3·78% N, 61·94% Br. ^{1}H-NMR spectrum (δ in ppm): 3·21 (s, 3 H, CH_3), 6·73 (d, 1 H arom., $J = 7$ Hz), 7·2—7·8 (m, 2 H arom.). IR spectrum (cm^{-1}): 535 m, 619 m, 661 w, 745 m, 810 s, 928 w, 935 w, 1 092 m, 1 326 m, 1 469 m, 1 480 s, 1 609 m, 1 760 s, 2 920 w. Mass spectrum (*m/z*, rel. intensity, %): 387 (2), 385 (8), 383 (8), 381 (2), 305 (33), 304 (66), 303 (33), 226 (100), 225 (28), 224 (100), 198 (8), 146 (9), 118 (19), 117 (19), 75 (15).

3-*Bromo*-1-*methyl*-2,3-*indoledione* (VIII): m.p. 173—174°C, ref.[18] 172—173°C. ^{1}H-NMR spectrum (δ in ppm): 3·23 (s, 3 H, CH_3), 6·79 (d, 1 H arom., $J = 7$ Hz), 7·6—7·9 (m, 2 H arom.). IR-spectrum (cm^{-1}): 580 w, 711 m, 814 s, 1 095 w, 1 166 w, 1 311 m, 1 357 w, 1 432 w, 1 460, w 1 609 m, 1 752 s. Mass spectrum (*m/e*, rel. intensity, %): 241 (100), 239 (100), 213 (81), 211 (81), 186 (87), 185 (85), 184 (87), 183 (83), 172 (27), 170 (27), 168 (27), 158 (21), 156 (25), 104 (21), 77 (52), 75 (44), 63 (58).

3-*Methoxy*-1,3-*dimethyl*-2-*indolinone* (IX): m.p. 73—75°C. For $C_{11}H_{13}NO_2$ (191·2) calculated: 69·09% C, 6·85% H, 7·32% N, 16·23% OCH_3; found: 69·06% C, 6·91% H, 7·28% N, 16·05% OCH_3. ^{1}H-NMR spectrum (in ppm): 1·54 (s, 3 H, C—CH_3), 3·02 (s, 3 H, OCH_3), 3·21 (s, 3 H, N—CH_3), 6·7—7·4 (m, 4 H, arom). IR spectrum (cm^{-1}): 906 w, 1 022 m, 1 068 w, 1 104 m, 1 112 m, 1 138 m, 1 243 m, 1 343 m, 1 373 m, 1 470 m, 1 491 m, 1 615 s, 1 734 s, 2 835 w, 2 890 w, 2 942 w, 3 000 w, 3 065 w. Mass spectrum (*m/z*, rel. intensity, %): 192 (12), 191 (80), 176 (53), 161 (94), 160 (100), 148 (69), 133 (37), 132 (60, 130 (37), 117 (24), 124 (20), 103 (20), 102 (20), 91 (22), 90 (90 (20), 89 (20), 77 (41).

3-*Hydroxy*-1,3-*dimethyl*-2-*indolinone* (X): m.p. 154—156°C, ref.[19] 157—159°C. ^{1}H-NMR spectrum (δ in ppm): 1·56 (s, 3 H, C—CH_3), 3·02 (s, 1 H, OH), 3·18 (s, 3 H, N-CH_3), 6·7—7·5 (m, 4 H arom.). IR-spectrum (cm^{-1}): 943 w, 1 031 w, 1 098 m, 1 120 w, 1 132 m, 1 220 m, 1 302w, 1 356 m, 1 382 m, 1 475 s, 1 498 m, 1 621 s, 1 716 s, 1 734 s, 2 980 w, 3 420 s, 3 580 w. Mass spectrum (*m/z*, rel. intensity, %): 178 (11), 177 (91), 162 (48), 149 (35), 135 (91), 134 (100), 132 (34), 116 (11), 106 (18), 91 (12), 78 (36), 77 (34).

3,5-*Dibromo*-1,3-*dimethyl*-2-*indolinone* (XI): ^{1}H-NMR spectrum (δ in ppm): 2·02 (s, 3 H, C—CH_3), 3·21 (s, 3 H, N—CH_3), 6·66 (d, 1 H arom., $J = 8$ Hz), 7·3—7·6 (m, 2 H arom.), IR-spectrum (cm^{-1}): 538 m, 578 w, 648 w, 811 s, 862 w, 882 m, 1 050 w, 1 110 m, 1 160 w, 1 235 w, 1 338 m, 1 363 m, 1 373 w, 1 425 w, 1 768 m, 1 490 s, 1 611 s, 1 743 s, 2 930 w, 2 980 w. Mass spectrum (*m/z*, rel. intensity, %): 321 (8), 319 (16), 317 (8), 241 (17), 240 (100), 239 (23), 238 (100), 225 (6), 223 (6), 161 (10), 160 (69), 150 (38), 131 (36), 130 (36), 108 (11), 107 (14), 79 (23), 77 (17). The compound was not analytically pure.

3-*Bromo*-1,2-*dimethylindole* (XII): m.p. 72—74°C, ref.[8] 73—74°C. ^{1}H-NMR spectrum (δ in ppm): 2·40 (s, 3 H, C—CH_3), 3·62 (s, 3 H, N—CH_3), 7·0—7·5 (m, 4 H arom.). Mass spectrum (*m/z*, rel. intensity, %): 226 (13), 225 (100), 224 (32), 223 (100), 222 (22), 144 (74), 143 (28), 129 (15), 128 (17), 116 (10), 115 (28), 102 (11), 77 (13), 75 (11), 63 (10).

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