# AZAINDOLE DERIVATIVES. 57.* DEHYDROGENATION OF SUBSTITUTED 5- AND 7-AZAINDOLINES WITH ACTIVATED MANGANESE DIOXIDE

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UDC 547.759.3'821:542.941.8

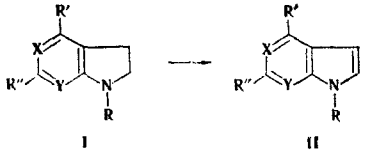
A number of 5- and 7-azaindolines were oxidized to the corresponding azaindoles by means of activated manganese dioxide. The dependence of the ease of dehydrogenation of 5- and 7-azaindolines by activated manganese dioxide on their oxidation potentials is demonstrated.

In recent years activated manganese dioxide has been used for the conversion of indoline compounds to indole derivatives [2, 3].

Preobrazhenskaya and co-workers have reported the use of this reagent also for the dehydrogenation of 1-[2,3,4-tri-O-acetyl-$\alpha$-L-arabinopyranosyl]-4-methyl-6-chloro-7-azaindoline [4]. In connection with the systematic study of the redox reactions of isomeric aza(diaza)indolines and indoles [5, 6] we made a more detailed study of the possibility of the use of activated manganese dioxide for the conversion of various substituted azaindolines to the corresponding azaindoles and determined the limits of applicability of this method.

The freshly prepared $\gamma$ form of manganese dioxide, obtained by the method in [7], or, in the case of more easily oxidized substances, activated manganese dioxide, obtained by the Attenborough method (in the latter case this is mentioned in the experimental section), was used as the oxidizing agent.

We investigated 5- and 7-azaindolines (I) with various substituents attached to the pyrroline nitrogen atom and the carbon atoms as the azaindoline derivatives. The investigated compounds had oxidation potentials over a broad range characterized by $E_{1/2}$ values from 0.9 to 1.86 V.



I II

a X=CH, Y=N, R=$C_6H_5$, R'=$CH_3$, R''=Cl; b X=N, Y=CH, R=$C_6H_5$, R'=H, R''=OH; c X=N, Y=CH, R=R'=R''=H; d X=CH, Y=N, R=$CH_3CO$, R'=$CH_3$, R''=Cl; e X=CH, Y=N, R=$C_6H_5$, R'=$CH_3$, R''=$(C_2H_5)_2NCH_2CH_2O$; f X=N, Y=C—CN, R=$C_6H_5CH_2$, R'=H, R''=Cl; g X=N, Y=C—CN, R=$C_6H_5CH_2$, R'=H, R''=OH; h X=N, Y=CH, R=R'=H, R''=OH

The oxidation was carried out in various solvents: carbon tetrachloride, benzene, and xylene. No strict regularities in the effect of the character of the indicated solvents on the course of the reaction were observed. The use of pyridine or chloroform (in order to increase the solubility of starting azaindolines I) as the solvent in the oxidation of $\gamma$-manganese dioxide did not give positive results: even in those cases where, for example, the oxidation of If with manganese dioxide in carbon tetrachloride occurred at room temperature for 15 h, the analogous process in pyridine gave only traces of IIf, and the azaindoline derivative was basically recovered unchanged. Deactivation of the oxidizing agent evidently occurs under the influence of pyridine and chloroform.

The addition of fresh portions of activated manganese dioxide accelerates the process. Removal of the water formed during the oxidation in a Dean–Stark apparatus does not have a significant effect on the oxidation.

*See [1] for communication 56.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 375-378, March, 1979. Original article submitted January 5, 1978; revision submitted July 18, 1978.


0009-3122/79/1503-0310$07.50 

As expected, the magnitude of the oxidation potential of the azaindoline compound was most important for the investigated reaction. The $E_{1/2}$ values of azaindoline compounds Ia-h were determined by polarography by the method described in [5]; the results are presented in the experimental section.

A comparison of the oxidation potentials ($E_{1/2}$) with the results of dehydrogenation of 5- and 7-azaindoline derivatives under the influence of activated manganese dioxide makes it possible to assert that this oxidizing agent is a stronger dehydrogenating agent than dichlorodicyanoquinone or chloranil. As noted in [6], chloranil oxidizes azaindoline derivatives that have $E_{1/2}$ values lower than 1.1 V, and the stronger oxidizing agent dichlorodicyanoquinone dehydrogenates azaindolines with $E_{1/2}$ values to 1.2 V. Activated $\gamma$-manganese dioxide is capable of dehydrogenating azaindolines with $E_{1/2}$ values up to 1.4 V (e.g., If with $E_{1/2}$ 1.35 V).

Substances with $E_{1/2}$ values greater than 1.4 V (e.g., Ib with $E_{1/2}$ 1.45 V, Ig with $E_{1/2}$ 1.61 V, and Ih with $E_{1/2} > 1.86$ V) cannot be converted to the corresponding azaindoles (IIb,g,h) even in the case of prolonged heating with activated $\gamma$-manganese dioxide and the addition of fresh portions of the oxidizing agent.

As noted in [5], azaindolines that have such $E_{1/2}$ values are not oxidized to azaindoles even when they are heated with sulfur up to 240°C or with selenium up to 300°C or in the case of thermal treatment with palladium. Activated manganese dioxide obtained both by the Attenborough method and by the Vereshchagin method is not only a more active dehydrogenating agent than the quinones normally used for this purpose, but, in contrast to the latter, it does not give complexes of the azaindole–hydroquinone type that hinder the isolation and purification of the reaction products. In this connection, the yields of azaindole compounds are higher in many cases in experiments with activated manganese dioxide than in the case of experiments with quinones.

## EXPERIMENTAL

The volt-ampere curves of the investigated compounds were recorded with a PA-101 polarograph (Yanagimoto, Japan). The $E_{1/2}$ values were determined by polarographic oxidation on a platinum rotating disk (1880 rpm) electrode (S = 0.031 $cm^2$) in an inert electrolyte (0.5 M $NaClO_4$ in ethanol) at 25.0 ± 0.1°C; the comparison electrode was a saturated calomel half cell, and the accuracy in the measurements was ±0.01 V. The experimentally found $E_{1/2}$ values were: Ia 0.92, Ib 1.45, Ic 0.95, Ie 0.95, If 1.35, Ig 1.61, and Ih > 1.86 V. The $E_{1/2}$ value of 1.07 V for Id was calculated from the correlation equation derived in [5]: $E_{1/2} = 0.8 + 0.37\sigma^+ + 0.14\sigma^*$ ($\sigma^+ = 0.114$, and $\sigma^* = 1.65$). The UV spectra of solutions of the azaindoline† and azaindole compounds were recorded with an EPS-3 spectrophotometer. The end of the dehydrogenation of azaindolines I was monitored from the disappearance of the peak of I on the gas-liquid chromatogram. A Pye–Unicam chromatograph with a catharometer as the detector and a 2.5 m by 4 mm glass column were used; the stationary phase was FS-1 elastomer applied in 3% amounts to silanized diatomite (80-100 mesh) the column temperature was 250°C, and the helium flow rate was 30 ml/min.

1-Phenyl-4-methyl-6-chloro-7-azaindole (IIa). A solution of 5.85 g (24 mmole) of azaindoline Ia [8] in 200 ml of xylene was refluxed with stirring for 5 h with 23 g of activated (by the Attenborough method) manganese dioxide, after which the precipitate was removed by filtration and washed with hot xylene. The residue after evaporation of the filtrate was vacuum distilled to give 4.73 g (82%) of azaindole IIa [9] with bp 187-188°C (3 mm) as colorless crystals with mp 71-72°C (from methanol). The product was quite soluble in benzene, xylene, and chloroform, slightly soluble in alcohols, and insoluble in water. UV spectrum, $\lambda_{max}$ (ε): C 69.2; H 5.6; Cl 14.2; N 11.5%. $C_{14}H_{11}ClN_2$. Calculated: C 69.3; H 4.6; Cl 14.6; N 11.5%.

1-Acetyl-4-methyl-6-chloro-7-azaindole (IId). This compound was obtained from 3.15 g (15 mmole) of 1-acetyl-4-methyl-6-chloro-7-azaindoline (Id) [10] under the same conditions and was purified by vacuum sublimation. The yield was 1.89 g (61%). The colorless crystals, with mp 119-120°C, were quite soluble in benzene, chloroform, and xylene, slightly soluble in alcohols, and insoluble in water. UV spectrum, λ (ε): 233 (17780), 256 nm (9400). Found: C 57.9; H 4.5; Cl 17.2; N 13.6%. $C_{10}H_9ClN_2O$. Calculated: C 57.6; H 4.41; Cl 17.0; N 13.4%.

1-Phenyl-4-methyl-6-(2'-diethylaminoethoxy)-7-azaindoline (Ie). A 6.1 g (25 mmole) sample of 1-phenyl-4-methyl-6-chloro-7-azaindoline (Ia) [8] was added to potassium alkoxide obtained from 2.1 g (55 mg-atom) of potassium and 21 ml (158 mmole) of diethylaminoethanol, and the mixture was heated at 180°C for 7 h. The excess diethylaminoethanol was removed by distillation, 30 ml of water was added to the residue, and the mixture was extracted with benzene. The benzene extract was washed with 4% hydrochloric acid, dried

†UV spectra for the corresponding azaindolines, $\lambda_{max}$ (ε): Ia 286 (19200), 329 nm (14500); Id 250 (12380), 300 nm (12380); If 223 (25500); 276 (16800), 331 nm (5500).

with potassium carbonate, and evaporated in vacuo. The residue was distilled with collection of the fraction with bp 204-206°C (2 mm) to give 6.07 g (75%) of azaindoline Ie as colorless crystals with mp 60-61°C (from alcohol). The product was quite soluble in ether, acetone, and ethyl acetate, slightly soluble in alcohols, and insoluble in water. UV spectrum, $\lambda(\varepsilon)$: 278 (15760), 331 nm (21060). Found: C 73.9; H 8.2; N 13.2%. $C_{20}H_{27}N_3O$. Calculated: C 73.8; H 8.4; N 12.9%. The hydrochloride was obtained as colorless crystals with mp 185-186°C. The product was soluble in chloroform, methanol, hot ethanol, and hot water but insoluble in acetone, ethyl acetate, and benzene. Found: C 66.4; H 8.0; Cl 9.7; N 11.6%. $C_{20}H_{27}N_3O \cdot HCl$. Calculated: C 66.4; H 7.8; Cl 9.8; N 11.6%.

1-Phenyl-4-methyl-6-(2'-diethylaminoethoxy)-7-azaindole (IIe). This compound was obtained from 3.25 g (10 mmole) of azaindoline Ie under the same conditions as in the preparation of IIa and was purified by vacuum distillation. The yield was 2.51 g (73%). The colorless crystals, with mp 55-56°C and bp 206-208°C (1 mm), were quite soluble in nonpolar solvents, less soluble in alcohols, and insoluble in water. UV spectrum, $\lambda_{max}(\varepsilon)$: 258 (15600), 330 nm (7040). Found: C 74.0; H 7.7; N 12.9%. $C_{20}H_{27}N_3O$. Calculated: C 74.3; H 7.8; N 13.0%.

1-Benzyl-6-chloro-7-cyano-5-azaindole (IIf). A 3-g (11.1 mmole) sample of azaindoline IIf [11] was dissolved in 1.5 liters of hot carbon tetrachloride, the solution was cooled to room temperature, and 20 g of activated $\gamma$-manganese dioxide was added with stirring in 5 g portions in the course of 15 min. The resulting precipitate was removed by filtration and washed with 100 ml of carbon tetrachloride, and the filtrate was evaporated to give 2.08 g (70%) of IIf as colorless crystals with mp 107-108°C (from cyclohexane). The product was quite soluble in benzene, chloroform, and xylene and slightly soluble in cyclohexane and water. UV spectrum, $\lambda_{max}(\varepsilon)$: 241 (29400), 302 nm (3530). Found: C 67.3; H 4.0; Cl 13.0; N 15.9%. $C_{15}H_{10}ClN_3$. Calculated: C 67.3; H 3.8; cl 13.2; N 15.7%.

Under the same conditions 5-azaindoline (Ic) [12] was converted to 5-azaindole (IIc), which was identified by comparison of the IR spectra and a mixed-melting-point determination with a genuine sample of 5-azaindole [12].

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