# OXIDATION OF 1,4-DIHYDROPYRIDINES

## II.* REACTIVITY DURING THE OXIDATION OF CHLORANIL

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The rate constants for the oxidation of 17 mono- and polynuclear 1,4-dihydropyridine derivatives with chloranil were determined. The constants obtained were compared with the results of fermentative and electrochemical oxidation.

There are studies [2, 3] available on the determination of the rate constant for the oxidation of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine with chloranil. In the oxidation [4] of a number of 1,4-dihydropyridines with a peroxidase – $H_2O_2$ system or with 2-(p-chlorobenzylidene)-1,3-indanedione [1], we have shown the inhibiting effect of an α substituent and the accelerating effect of α-methyl groups. The effect of a β substituent depended both on the nature of the substituent and on the hydrogen acceptor.

In the present study we have determined the rate constants for the oxidation of 1,4-dihydropyridines with chloranil. Primarily previously described compounds were used as the 1,4-dihydropyridine derivatives (both mono- and polynuclear); XI and XV were obtained by a known method [5], while III was synthesized from benzoylacetone and urotropin. The UV spectra of XI and XV coincide with the UV spectra of their analogs (there is a characteristic deepening of color in alkaline media), the UV spectrum of III coincides with the spectrum of the known 4-methyl derivative (V), and only the 4-methyl group causes a hypsochromic shift of the long-wave maximum. This was also observed [6] for the β-acetyl analogs of these compounds.

Just as in fermentative oxidation [4], the reactions were carried out at 37°C. The concentration was measured spectrophotometrically at the long-wave absorption maximum characteristic for 1,4-dihydropyridines, which vanishes on oxidation. In this case, the polynuclear 1,4-dihydropyridine derivatives (IX-XVII) even undergo a sharp change in color [5]. The results, which are presented in Tables 1 and 2, show that the investigated reaction is second-order; this is in agreement with the data for II [3]. Difficulties arose because of the slight solubility of some of the compounds (particularly XIII, XIV, XV, and XVII); this possibly reduced the accuracy of the measurements.

In a comparison of the results with approximate data [1], complete coincidence of the indexes that characterize the effect of the structure on the reactivity was established, even though a different solvent was used. On comparison of the results of the oxidation of 1,4-dihydropyridine derivatives by chemical, polarographic [7], and fermentative [4] methods, it is seen that, regardless of the oxidation mechanism, γ-unsubstituted compounds are the most active. The extreme ease of the oxidation of X indicates that the absence of β-electron-acceptor groups lowers the stability of 1,4-dihydropyridine. This is in agreement with the known data on the stability of such compounds [8, 9]. For the same reason, XI, i.e., a β-phenylcarbamoyl derivative in which the stabilizing effect of the carbonyl group is weakened, is extremely active.

A comparison of the effect of β substituents shows that compounds that have an acetyl or ethoxycarbonyl group are more active than compounds that have a cyano group. In the oxidation with chloranil, just as in electrochemical oxidation [7], compounds that have a β-acetyl group are oxidized more readily than compounds that have a β-ethoxycarbonyl group. The reverse activity ratio is observed in the fermen-

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*See [1] for communication I.

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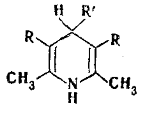
TABLE 1. Rate Constants for the Oxidation of 1,4-Dihydropyridine Derivatives (I-VIII) with Chloranil in Benzene at 37°C


I-VIII

| Compound | R | R′ | Synthetic method | Initial concn. ratio of I-VIII* and chloranil | Measurement made at λ, nm | Exptl. time, min | Am. of I-VIII consumed in reaction, % | $k \cdot 10^2$, liter · $mole^{-1}$ · $sec^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| I | $COCH_3$ | H | 10 | 1 : 1 | 393 | 55 | 68,1 | 630 |
| II | $COOC_2H_5$ | H | 11 | 1 : 1 | 360 | 63 | 63,3 | 450 |
| III | $COC_6H_5$ | H | † | 1 : 3 | 385 | 65 | 92,2 | 290 |
| IV | CN | H | 12 | 1 : 3 | 342 | 309 | 78,4 | 33 |
| V | $COC_6H_5$ | $CH_3$ | 13 | 1 : 3 | 370 | 276 | 62,5 | 23 |
| VI | $COCH_3$ | $CH_3$ | 14 | 1 : 3 | 379 | 327 | 14,3 | 2,6 |
| VII | $COOC_2H_5$ | $CH_3$ | 15 | 1 : 3 | 354 | 443 | 15 | 2,1 |
| VIII | $COOC_2H_5$ | $C_6H_5$ | 16 | 1 : 3 | 333 | 315 | 10 | 1,8 |

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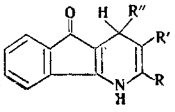
* The initial concentration of I-VIII was $10^{-4}$ M.

† The description of the synthesis is given in the experimental section.

TABLE 2. Rate Constants for the Oxidation of (IX-XVII) 5-Oxo-1,4-dihydroindeno[1,2-b]pyridine Derivatives with Chloranil in Benzene at 37°C


IX-XVII

| Compound | R | R′ | R″ | Synthetic method | Initial concn. of IX-XVII, (mole/liter) · $10^5$ | Initial ratio of the concn. of IX-XVII and chloranil | Measurement made at λ, nm | Exptl. time, min | Amount of IX-XVII consumed in the reaction, % | $k \cdot 10^2$, liter · $mole^{-1}$ · $sec^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| IX | $CH_3$ | $—COOC_2H_5$ | H | 17 | 10,0 | 1 : 3 | 467 | 50 | 90,5 | 415 |
| X | $C_6H_5$ | H | $C_6H_5$ | 8 | 10,0 | 1 : 3 | 451 | 16 | 87 | 960 |
| XI | $CH_3$ | $—CONHC_6H_5$ | $C_6H_5$ | — ‡ | 5,0 | 1 : 3 | 451 | 110 | 73,5 | 190 |
| XII | $CH_3$ | $—COC_6H_5$ | $C_6H_5$ | 5 | 10,0 | 1 : 3 | 447 | 100 | 75,7 | 94 |
| XIII | $CH_3$ | $—COCH_3$ | $C_6H_5$ | 5 | 3,7 | 1 : 8 | 455 | 84 | 70,4 | 86 |
| XIV | $CH_3$ | $—COOC_2H_5$ | $C_6H_5$ | 5 | 2,3 | 1 : 13 | 452 | 101 | 76 | 82 |
| XV | $CH_3$ | —CN | $C_6H_5$ | — ‡ | 4,5 | 1 : 7 | 445 | 121 | 62,3 | 45 |
| XVI* | (o-)$—C_6H_4—CO—$ |  | $C_6H_5$ | 18 | 10,0 | 1 : 3 | 500 | 420 | 86,6 | 33 |
| XVII† | $—CH_2C(CH_3)_2CH_2CO—$ |  | $C_6H_5$ | 19 | 2,0 | 1 : 15 | 447 | 405 | 50 | 14 |

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* 11-Phenyl-10,12-dioxo-5,10-dihydrodiindeno[1,2-b:2',1'-e]pyridine.

† 7,7-Dimethyl-10-phenyl-9,11-dioxo-5,6,7,8,9,10-hexahydro-11H-indeno[1,2-b]quinoline.

‡ The description of the synthesis is given in the experimental section.

tative oxidation of dihydropyridines [4] and in the reduction of ylideneindanediones [1]. When β-benzoyl groups are introduced, electrochemical oxidation [7] in all cases proceeds more readily than in the case of acetyl analogs. The same order is observed in chemical oxidation in the case of V and VI and also XII and XIII, but γ-unsubstituted compound III is oxidized with greater difficulty than its acetyl analog (I), probably because of steric effects.

The effect of the o-benzoylene group (see Table 2) remains unclear. The introduction of one substituent in place of the carbethoxy group gives contradictory results: the reactivity of the γ-unsubstituted compounds (II and IX) falls, and the reactivity of the γ-phenyl-substituted compounds (VIII and XIV) increases. The introduction of a second substituent (XVI) lowers the reactivity.

## EXPERIMENTAL

2-Methyl-4-phenyl-3-cyano-5-oxo-1,4-dihydroindeno[1,2-b]pyridine (XV). A solution of 1.17 g (5 mmole) of 2-benzylidene-1,3-indanedione and 0.45 g (5.5 mmole) of β-aminocrotonitrile in 15 ml of glacial acetic acid was refluxed for 5 min. The mixture was cooled, and the precipitate was removed by filtration and washed with acetic acid to give 1.3 g (87%) of an orange substance with mp 247-248° (from acetic acid). Found: C 80.5; H 4.7; N 9.4%. $C_{20}H_{14}N_2O$. Calculated: C 80.5; H 4.7; N 9.4%. UV spectrum, $\lambda_{max}$, nm (log ε), in ethanol: 229 shoulder (4.33), 234 (4.37), 253 shoulder (4.38), 260 (4.38), 302 shoulder (3.64), 320 (3.62), 343 (3.67), 467 (3.40); in ethanol + NaOH: 241 shoulder (4.34), 245 (4.35), 270 shoulder (4.09), 278 (4.10),312 (3.79), 333 (3.66), 368 (3.64), 533 (3.79), 563 (3.81).

2-Methyl-4-phenyl-3-phenylcarbamoyl-5-oxo-1,4-dihydroindeno[1,2-b]pyridine (XI). This compound (red substance, in 50% yield), with mp 255-260° (from acetic acid), was similarly obtained from 2-benzylidene-1,3-indanedione and β-aminocrotonic acid anilide. Found: C 78.9; H 5.5; N 7.1%. $C_{25}H_{20}N_2O_2$. Calculated: C 78.9; H 5.3; N 7.4%. UV spectrum, $\lambda_{max}$, nm (log ε), in ethanol: 233 (4.40), 263 (4.38), 301 shoulder (3.82), 315 shoulder (3.70), 345 (3.54), 475 (3.45); in ethanol + NaOH; 236 (4.45), 247 shoulder (4.42), 281 shoulder (4.11), 317 (3.96), 370 shoulder (3.68), 530 shoulder (3.72).

2,6-Dimethyl-3,5-dibenzoyl-1,4-dihydropyridine (III). A solution of 1.5 g (0.011 mole) of urotropin, 4.2 g (0.05 mole) of ammonium acetate, and 19.5 g (0.12 mole) of benzoylacetone in 60 ml of ethanol was refluxed for 1 h. It was then cooled, and the bright-yellow precipitate was removed by filtration to give 12.2 g (64%) of III with mp 195-200° (from dioxane). Found: C 79.4; H 6.0; N 4.1%. $C_{21}H_{19}NO_2$. Calculated: C 79.4; H 6.0; N 4.4%. UV spectrum in ethanol, $\lambda_{max}$, nm (log ε): 252 (4.16), 315 (3.58), 413 (3.83).

Measurement of the Reaction Rates. Solutions of tetrachloro-p-benzoquinone (chloranil) and 1,4-dihydropyridine derivatives (I-XVII, see Tables 1 and 2) were prepared. The temperature of the solutions was brought up to 37° in a thermostat, and the solutions were mixed. The changes in the optical density of the reaction mixture were measured with an SF-4 spectrophotometer with a thermostated cuvette. The starting data and the results of the measurements are combined in Tables 1 and 2.

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