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ACID HYDROLYSIS OF N-METHYL DERIVATIVES OF 4-PHENYL-5-OXO-4,5-DEHYDROINDENO[1,2-b]PYRIDINE

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The splitting of the dihydropyridine ring of N-methyl-substituted 4-phenyl-5-oxo-4,5-dihydroindeno[1,2-b]pyridine in an acid medium takes place at the C—N bond. During the splitting of 1,2-dimethyl-4-phenyl-4,5-dihydroindeno[1,2-b]-pyridine, 4-phenyl-4-(indane-1,3-dion-2-yl)butan-2-one is formed, while in the case of the 3-ethoxycarbonyl derivative of indenopyridine, together with the Michael retroreaction leading to 2-benzylideneindane-1,3-dione, a recyclization of the intermediate product into a derivative of dihydroindeno-2-pyridone takes place.

It is known [1] that during alkylation, 5-oxo-1H-4,5-dihydroindeno[1,2-b]pyridines form C- and N-alkylation products, i.e., they exhibit properties characteristic of enamino ketones In the present work, it was shown that splitting of the dihydropyridine ring of 1,2-dimethyl-4-phenyl-5-oxo-4,5-dihydroindeno[1,2-b]pyridine (Ia) and its 3-ethoxycarbonyl derivative (Ib) in an acid medium proceeds as an acid hydrolysis of enamines.

According to the generally accepted scheme, the hydrolysis of enamines includes the protonation of the β-carbon atom, followed by the addition of water to the α-carbon atom and cleavage of the C—N bond. Since the molecule of dihydroindenopyridine I contains two fragments, which are enamine systems: $C_{(4a)}$—$C_{(9b)}$—N and $C_{(3)}$—$C_{(2)}$—N, a cleavage of both the N—$C_{(9b)}$ and N—$C_{(2)}$ bond is possible with the formation of intermediate products A and B. However, these primary hydrolysis products were not detected in the reaction mixture, but products of their further transformation were isolated. Thus, during the hydrolysis of 1,2-dimethyl-3-ethoxycarbonyl-4-phenyl-5-oxo-4,5-dihydroindeno[1,2-b]pyridine (Ib), 2-benzylideneindane-1,3-dione (II), 2-benzylindane-1,3-dione (III), and 1-methyl-3-acetyl-4-phenyl-2,5-dioxo-2,5-dihydroindeno[1,2-b]pyridine (IV) were detected. Indenopyridone IV is an oxidized form of 1-methyl-3-acetyl-4-phenyl-2,5-dioxo-2,3,4,5-tetrahydroindeno[1,2-b]pyridine (V), formed as the result of an intramolecular interaction of an ester group with the 1-methylamino functional group of the intermediate product B. Structure IV was confirmed by spectral methods and alternative synthesis: cyclization of N-monomethyl α-acetyl-β-phenyl-β-(indane-1,3-dion-2-yl)propionamide (VI) into 2,5-dioxo-2,3,4,5-tetrahydroindenopyridine

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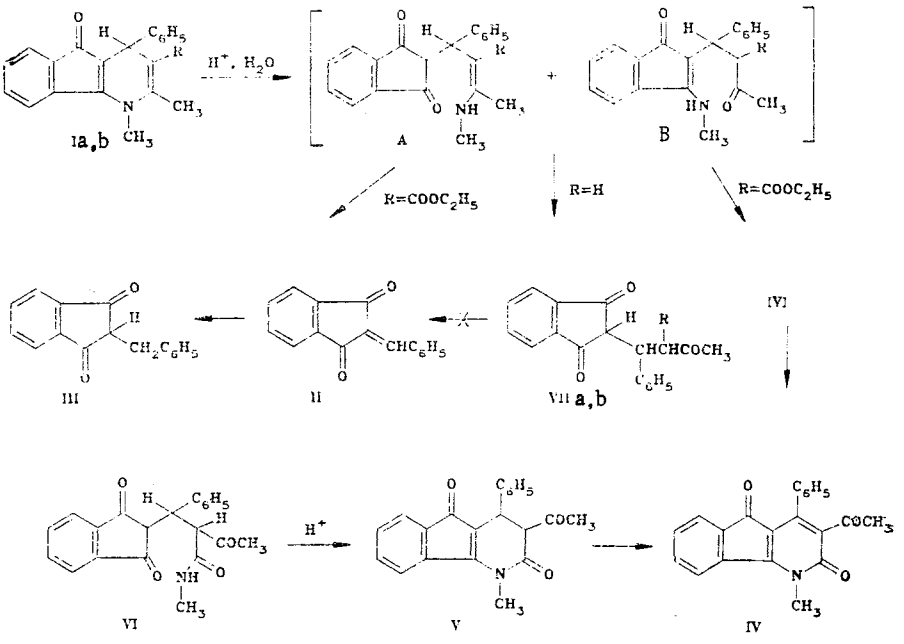
(V) and oxidation of the latter. Cyclization of monoamide (VI) proceeds similarly to the cyclization of diamides of α-(indane-1,3-dion-2-yl)benzylmalonic acid [2], but at elevated temperature, instead of cyclization, the Michael retroreaction with the formation of compound II takes place.

If the formation of indenopyridone IV unequivocally confirms the cleavage of the N—C(2) bond during the hydrolysis of compound Ib, then compound II can formally be obtained in this reaction by splitting of both the intermediate compound A (hydrolysis at the N—C(9b) bond) and B (hydrolysis at the N—C(2) bond), followed by the replacement of the $NHCH_3$ group of the OH group. However, the formation of 2-benzylideneindane-1,3-dione from the intermediate product B is excluded, since 4-phenyl-4-(indane-1,3-dion-2-yl)-3-ethoxycarbonylbutan-2-one (VIIb) does not change under the conditions of the acid hydrolysis of Ib. Hence, it can be concluded that during the hydrolysis of compound Ib, 2-benzylideneindane-1,3-dione (II) is formed as the result of the Michael retroreaction from the intermediate product A, arising after the cleavage of the N—C(9b) bond. Compound III should be regarded as a reduction product of compound II. Tetrahydro-2-oxopyridine V, a precursor of pyridone IV, isolated from the reaction mixture, and dihydroindenopyridine Ib can serve as reducing agents, since both the ability of hydrogenated pyridones to reduce benzylideneacetophenone [3], and the ability of the 1H analog of compound Ib to reduce 2-arylideneindane-1,3-diones [4] are known. It is impossible to unequivocally determine the direction of the process, for example, by the reduction of dione II by dihydroindenopyridine Ib in the presence of HCl, because of its acid hydrolysis. During the reduction of compound II by tetrahydropyridone V in an acidified alcoholic medium, as well as in its reduction by dihydroindenopyridine Ib in acetic acid, the presence of 2-benzylindane-1,3-dione (III) in the reaction mixture was confirmed by liquid chromatography. A quantitative ratio of the hydrolysis products of Ib (IV:II + III) indicates a different rate of hydrolysis of the N—C(2) and N—C(9b) bonds and leads to the conclusion that the cleavage of the N—C(9b) bond proceeds more easily.



Ia, VIIa R=H; б R=$COOC_2H_5$

The main product of the hydrolysis of compound Ia is 4-phenyl-4-(indane-1,3-dion-2-yl)-butan-2-one (VIIa). The absence of compound II from the hydrolysis products of Ia shows that the Michael retroreaction does not take place. If it is proved that during the hydrolysis of compound Ib, the splitting of the dihydropyridine ring proceeds with the participation of the two enamine systems (both at the N—C(9b) and at the N—C(2) bond), then the formation of compound VIIa as the result of splitting of derivative Ia does not indicate a cleavage of only one given bond. In the hydrolysis of compound Ia with a cleavage of the N—C(2) bond, the intermediate product B cannot recyclize, and replacement of the $NHCH_3$ group by an OH group in products A and B leads to the formation of derivative VIIa.

The data obtained confirm the enamine character of 1,4-dihydropyridine system. It is not excluded that also the previously noted instability of certain N-methyldihydropyridines in an acid medium [5] can be explained by a similar hydrolysis.

EXPERIMENTAL

The PMR spectra were run on a Bruker WH-90 spectrometer, using TMS as internal standard, and the IR spectra on a Perkin-Elmer 580 B spectrophotometer in Nuiol; the mass spectra were measured on a MS-50 AEI mass spectrometer at an energy of the ionizing electrons at 70 eV. Compounds Ia, b were obtained according to [1].

Hydrolysis of 1,2-dimethyl-3-ethoxycarbonyl-4-phenyl-5-oxo-4,5-dihydroindeno[1,2-b]-pyridine (Ib). A 3.59 g (10 mmoles) portion of compound Ib is dissolved in 200 ml of ethanol, 40 ml of water and 8.8 ml (100 mmoles) of concentrated HCl are added, and the mixture is boiled for 2 h. It is then cooled, and 0.93 g of 1-benzylideneindane-1,3-dione (II) is filtered. The filtrate (F) is diluted with 1 liter of water and extracted by ether (4 × 200 ml). The ether extracts are extracted by a 4% aqueous solution of NaOH (5 × 200 ml). After evaporation, another 0.2 g of compound II is obtained from the ether solution, the total yield of II being 48%. The alkaline aqueous solution is acidified by dilute HCl (1:1) and extracted by ether (4 × 200 ml). The ether extract is washed with water, dried and evaporated. The residue is recrystallized from methanol to yield 0.65 g (27%) of 2-benzylindane-1,3-dione (III). According to physicochemical characteristics, compounds II and III are identical with authentic samples of 2-benzyl- [6] and 2-benzylideneindane-1,3-diones [7]. The acid aqueous layer (filtrate F) after the extraction of compounds II and III, is made alkaline by a NaOH solution to pH 9-10 and extracted by ether (3 × 200 ml). The ether layer is washed with water, dried, and evaporated. The residue is chromatographed on a column with silica gel (L100/160), eluting first with a 5:1 chloroform–acetone mixture, and then with a 9:7:1 chloroform–hexane–acetone mixture. A yellow-orange fraction is collected. Yield, 0.56 g (18%) of compound IV, mp, 183°C (from methanol). IR spectrum: 1715, 1710, 1695 (CO), 1642 cm^{-1} (C=C). PMR spectrum (DMSO): 2.18 (s, 3H, $COCH_3$); 3.97 (s, 3H, NCH_3); 7.13-7.76 (m, 8H) and 7.96-8.09 ppm (m, 1H, aromatic protons). Mass spectrum, m/z, %: 329 (51) $[M]^{+\cdot}$, 328 (33) $[M-H]^+$, 314 (100) $[M-CH_3]^+$, 300 (8) $[M-CO-H]^+$, 286 (17) $[M-COCH_3]^+$, 258 (10) $[M-COCH_3-CO]^+$, 195 (16). Found, %: C 76.4; H 4.8; N 4.4. $C_{21}H_{15}NO_3$. Calculated, %: C 76.4; H 4.6; N 4.3.

N-Monomethyl α-acetyl-β-phenyl-β-(indane-1,3-dion-2-yl)propionamide (VI) is obtained by condensation of equimolar amounts of benzalindanedione and N-monomethyl acetoacetamide in the presence of a 3% sodium methylate, in analogy with [8]. Mp, 112-114°C (from ethanol). PMR spectrum ($CDCl_3$): 2.42 (s, 3H, $COCH_3$); 2.52 (d, 3H, NCH , J_{NH-CH_3} = 5.0 Hz); 3.42 (d, 1H, 2-H, $J_{2H-\beta H}$ = 4.5 Hz); 4.20 (m, 1H, β-H); 4.77 (d, 1H, α-H, $J_{\beta H-\alpha H}$ = 13.0 Hz); 6.16 (m, 1H, NH); 7.08 (s, 5H, C_6H_5); 7.61-7.96 ppm (m, 4H, H of indene ring).

1-Methyl-3-acetyl-4-phenyl-2,5-dioxo-2,3,4,5-tetrahydroindeno[1,2-b]pyridine (V) is obtained by cyclization of 0.70 g (20 mmoles) of amide VI in 25 ml of concentrated HCl at 20°C (12 h). Yield, 0.36 g (55%). Red crystals, mp 142-143°C (from methanol). Mass spectrum, m/z, %: 331 (7) $[M]^{+\cdot}$, 329 (3) $[M-H_2]^{+\cdot}$, 314 (6) $[M-H_2-CH_3]^+$, 302 (12) $[M-CO-H]^+$, 288 (100) $[M-COCH_3]^+$, 260 (6) $[M-COCH_3-CO]^+$, 254 (31) $[M-C_6H_5]^+$, 236 (15) $[M-C_6H_5-H_2O]^+$, 212 (6). Found, %: C 76.0; H 5.5; N 4.3. $C_{21}H_{17}NO_3$. Calculated, %: C 76.1; H 5.2; N 4.2.

1-Methyl-3-acetyl-4-phenyl-2,5-dioxo-dihydroindeno[1,2-b]pyridine (IV). A 0.4 g of sodium nitrite is gradually added at 40°C to 0.1 g of compound V in 5 ml of glacial acetic acid. The reaction mixture is diluted with 100 ml of water, and a yellow-orange precipitate is filtered and recrystallized from methanol. Pyridone IV monohydrate is obtained, which loses water at 110°C. After drying in vacuo, the synthesized product is identical in its physicochemical characteristics with an authentic sample of pyridone IV, isolated during the hydrolysis of Ib.

Hydrolysis of 1,2-dimethyl-4-phenyl-5-oxo-4,5-dihydroindeno[1,2-b]pyridine (Ia). A 0.9 g portion (3 mmoles) of compound Ia is dissolved in 65 ml of ethanol, 12.5 ml of water and 2.76 ml (30 mmoles) of concentrated HCl are added, and the mixture is boiled for 15 min. It is then cooled, diluted with 300 ml of water, and extracted by ether (4 × 150 ml). The ether extracts are extracted by 4% aqueous solution of NaOH (4 × 200 ml). The alkaline aqueous solution is acidified by hydrochloric acid, and extracted by ether (5 × 150 ml). The ether extracts obtained are washed with water, dried, and evaporated. The residue is recrystallized from methanol. Yield, 0.75 g (82%) of pure dione VII. According to the data of IR and PMR spectra and elemental analysis, the product obtained is identical with an authentic sample synthesized according to [9].

Reduction of 2-benzylideneindane-1,3-dione (II) by Tetrahydropyridine (V). A 0.04 ml portion of concentrated HCl is added to a solution of 0.12 g (500 mmoles) of compound II and 0.17 g (500 mmoles) of compound V in 10 ml of 80% ethanol, and the mixture is boiled for 20 h. The reaction mixture is diluted with water and extracted by chloroform (2 × 30 ml). The chloroform extract is dried and evaporated. According to the data of liquid chromatography (Zorbah SIL; ethyl acetate—hexane, 35:15), the residue contains 49% of 2-benzylindane-1,3-dione III.

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1,2,5-TRIMETHYL-4-(p-HYDROXYARYL)-Δ^3-TETRAHYDROPYRIDINES AND THEIR SPATIAL STRUCTURE

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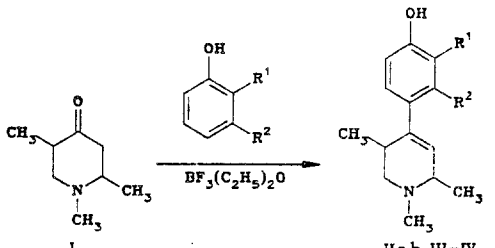
The condensation of 1,2,5-trimethylpiperidine-4-one with phenol and isomeric cresols yields 1,2,5-trimethyl-4-(p-hydroxyphenyl)- and (p-hydroxytolyl)-Δ^3-tetrahydropyridines, the structure and conformation of which have been studied by proton NMR spectroscopy.

The condensation of γ-piperidones with phenol (cresols) is of interest for the preparation of piperidine derivatives containing hydroxyphenyl groups in the γ-position. Compounds of this type are examined for their physiological activity [1].

We have studied the compounds formed by condensation of 1,2,5-trimethylpiperidine-4-one (I) with phenol and isomeric cresols in the presence of boron trifluoride etherate. In all cases, the compounds obtained were dehydration products of 1,2,5-trimethyl-4-(p-hydroxyaryl)-piperidine-4-ones.



I — IIa,b, III–IV

II a,b $R^1=R^2=H$; III $R^1=H$, $R^2=CH_3$; IV $R^1=CH_3$, $R^2=H$

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