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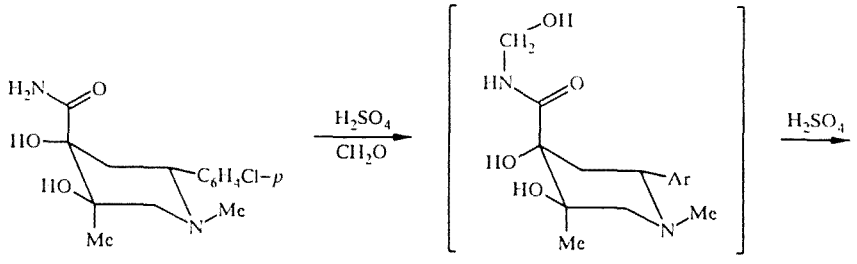
SYNTHESIS OF SPIROCYCLIC 1,3-DIOXOLAN-4-ONES FROM α-HYDROXYAMIDES

F. F. Lakhvich and L. S. Stanishevskii

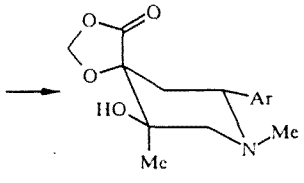
It is shown that α,β-dihydroxypiperidine-4-carboxyamides in reaction with formaldehyde in concentrated sulfuric acid is converted to the corresponding 1,3-dioxolan-4-ones.

It is known that 1,3-dioxolan-4-ones are obtained by the reactions of a-hydroxyacids and aldehydes under conditions of acid catalysis [1-3]. During studies of the synthesis of derivatives of hydroxypiperidinecarboxylic acids [4, 5], which are inhibitors and agonists of the synthesis of γ-aminobutyric acid [6], we observed that α-hydroxyamides can also be converted to 1,3-dioxolan-4-ones.

Thus, the reaction of diastereomeric 3e,4-dihydroxy-1e,3a-dimethyl-6e-[4-chlorophenyl]piperidine-4-carboxyamides I or II with paraformaldehyde, metaformaldehyde, or methylal in concentrated sulfuric acid for 50-60 h at 20-25°C gives the corresponding 1,3-dioxo-8-azaspiro[4,5]decane-4-ones V or VI. Intermediate compounds are products of the first addition of formaldehyde at the nitrogen atom of the amide group, N-hydroxymethylamides III or IV, which can be isolated from the reaction mixture some 30-40 min after the start of the process with yields of about 85%. Holding compounds III or IV in H_2SO_4 also leads to dioxolanones V or VI. This shows that the initial amides are not hydrolyzed to the corresponding hydroxyacids under the reaction conditions in the absence of a source of formaldehyde.



I, II III, IV



V, VI

III– VI Ar = C_6H_4Cl-*p*

The structure of the compounds prepared was established by IR and ^{1}H-NMR spectroscopy.

Thus, in the IR spectra of compounds III and IV absorption bands were found at 1700-1720 cm^{-1}, which correspond to the carbonyl stretching vibrations of the amide groups. In the case of compounds V and VI, vibrational bands from the carbonyl groups were found at 1800 cm^{-1}, which confirms unambiguously the formation of dioxolan-4-ones [2].

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In the ^{1}H-NMR spectra of compounds III and IV in $CDCl_3$, there are signals from the protons of the hydroxyamide group present as three quartets in the expected regions. Here, the double resonance method in DMSO-D_6 (with no exchange of the hydroxyl group proton) revealed an interaction of the CH_2 group protons with the amide and hydroxyl group protons. In the ^{1}H-NMR spectra of 1,3-dioxolan-4-ones V and VI in $CDCl_3$, the protons of the dioxolane methylene groups present two singlets (at 5.47 and 5.62 ppm for compound V and 5.54 and 5.67 ppm for compound VI) with SSCC < 0.5 Hz, which is in agreement with the literature values for related systems [7].

EXPERIMENTAL

The ^{1}H-NMR spectra of solutions of the synthesized compounds in $CDCl_3$ and DMSO-D_6 were obtained on a Bruker AC-200 spectrometer. The IR spectra of compounds III-VI in CCl_4 (10^{-3} M) were recorded on a Specord IR-75 spectrometer. The course of reaction and the purity of the products were monitored on Kieselgel TLC plates.

The elemental analyses agreed with the calculated values.

3e,4e-Dihydroxy-1e-3a-dimethyl-6e-[4-chlorophenyl]piperidine-4a-[N-hydroxymethyl]carboxyamide (III, $C_{15}H_{21}ClN_2O_4$). To a solution of 0.5 g of amide (1.7 mmol) in 1.2 ml of 95% H_2SO_4 is added 0.1 g of paraformaldehyde with constant stirring. The reaction mixture is held at 20-25°C for 30 min (monitor by TLC) and 5 g of finely crushed ice is then added. The mixture is neutralized with 28% aqueous ammonia and extracted with ethyl acetate. The resultant solution is dried with Na_2SO_4, the solvent evaporated off under reduced pressure, and the residue crystallized from a 1:1 toluene:hexane mixture to give 0.45 g of compound III (84% yield), mp 160-161°C. IR spectrum: 3600, 3440, 1720, 1700 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1.62 (3H, s, C−CH_3); 1.68 (1H, dd, J = 13.5; 11.5 Hz, 5-H_a); 1.98 (3H, s, N−CH_3); 2.46 (1H, d, 2-H_e); 2.54 (1H, dd, J = 13.5; 3.5 Hz, 5-H_a); 2.86 (1H, d, 2-H_a); 2.94 (1H, dd, J = 11.5; 3.5 Hz, 6-H_a); 4.92 (1H, dd, J = 9.0; 2.0 Hz, N−CH−O); 5.16 (1H, dd, J = 9.0; 2.5 Hz, N−CH−O); 6.52 (1H, m, N−H); 7.23-7.30 ppm (4H, m, Ar).

3e,4a-Dihydroxy-1e,3a-dimethyl-6e-[4-chlorophenyl]piperidine-4e-[N-hydroxymethyl]carboxyamide (IV, $C_{15}H_{21}ClN_2O_4$) is obtained analogously in an 82% yield, mp 149-150°C. IR spectrum: 3625, 3600, 3400, 1700 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1.52 (3H, s, C−CH_3); 1.94 (1H, dd, J = 15.0; 3.0 Hz, 5-H_e); 2.09 (3H, s, N−CH_3); 2.38 (1H, dd, J = 15.0; 12.0 Hz, 5-H_a); 2.53 (1H, d, 2-H_e); 2.84 (1H, d, 2-H_a); 3.15 (1H, dd, J = 12.0; 3.0 Hz, 6-H_a); 4.69 (1H, d, J = 6.0; 10.5 Hz, N−CH−O); 4.82 (1H, dd, J = 7.0; 10.5, N−CH−O); 7.61 (1H, m, N−H); 7.24-7.38 ppm (4H, m, Ar); (DMSO-D_6): 4.50 (2H, m, N−CH_2−O); 5.20 (1H, s, OH_{ring}); 5.28 (1H, s, OH_{ring}); 5.56 (1H, m, CH_2−OH); 8.52 ppm (1H, m, N−H).

(5R6R, 5S6S) 1,3-Dioxa-8-azaspiro[4,5]-6e-hydroxy-6a,8e-dimethyl-9e-(4-chlorophenyl)decane-4-one (V, $C_{15}H_{18}ClNO_4$). A solution of 1.1 g (35 mmol) of hydroxyamide I in a mixture of 5 ml of 95% sulfuric acid and 2 ml of metaformaldehyde is held at 20-25°C for 60 h. The reaction mixture is then poured onto 10 g of ice, neutralized with 28% aqueous ammonia, and extracted with ether. The resultant solution is dried with Na_2SO_4, and the solvent evaporated off under reduced pressure. After crystallization from a 6:1 hexane−ether mixture, 0.85 g of dioxolane V (75%) is obtained, mp 97-98°C. IR spectrum: 3580, 3425, 1790 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): 1.63 (3H, s, C−CH_3); 1.87 (1H, dd, J = 13.5; 11.5 Hz, 10-H_a); 1.94 (1H, dd, J = 13.5; 4.5 Hz, 10-H_e); 2.05 (3H, s, N−CH_3); 2.68 (1H, d, 7-He); 3.04 (1H, d, 7-H_a); 3.60 (1H, dd, J = 11.5; 4.5 Hz, 9-H_a); 5.47 (1H, s, O−CH−O); 5.62 (1H, s, O−CH−O); 7.24-7.32 ppm (4H, m, Ar).

(5S6R, 5R6S) 1,3-Dioxa-8-azaspiro[4,5]-6e-hydroxy-6a,8e-dimethyl-9e-(4-chlorophenyl)decane-4-one (VI, $C_{15}H_{18}ClNO_4$). To a solution of 0.5 g of hydroxyamide II in 1.5 ml of sulfuric acid is added 0.05 g of paraformaldehyde with constant stirring. The reaction mixture is held at 20-25°C for 65 h, then poured onto 5 g of ice, neutralized with 28% aqueous ammonia, and extracted with ether. After the solvent is distilled off under reduced pressure, the oily residue is chromatographed on a silica gel column with 1:2 tetrachloromethane:ethyl acetate to obtain 0.3 g of dioxolane VI (58%), mp 102-103°C. IR spectrum: 3600, 3570, 1800, 1785 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$): 1.72 (3H, s, C−CH_3); 1.83 (1H, dd, J = 14.0; 3.5 Hz, 10-H_e); 2.02 (3H, s, N−CH_3); 2.10 (1H, dd, J = 14.0; 11.0 Hz, 10-H_a); 2.58 (1H, d, 7-H_e); 2.70 (1H, d, 7-H_a); 3.14 (1H, dd, J = 11.0; 3.5 Hz, 9-H_a); 5.54 (1H, s, O−CH−O); 5.67 (1H, s, O−CH−O); 7.23-7.34 ppm. (4H, m, Ar).

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