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SYNTHESIS OF 3'-AROYL-4'-HYDROXYSPIRO-[INDOLE-3,2'-FURAN]-2,5'(1H)-DIONES

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It was found that adducts of 3'-aroyl-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-diones with tetramethylguanidine are formed when equimolar amounts of methyl aroylpyruvates, isatin, and N,N,N',N'-tetramethylguanidine are heated briefly in dioxane.

Keywords: 3'-aroyl-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-diones, methyl 4-aroylpyruvates, isatin, tetramethylguanidine.

It is known that the reaction of acylpyruvic esters with a mixture of an aromatic aldehyde and an alkylamine leads to the formation of 4-acyl-1-alkyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones [1]. If the aromatic aldehyde is replaced by ninhydrin alkylammonium 4-acetyl-2,1',3'-trioxospiro[2,5-dihydrofuran-5,2'-indane]-olates are formed [2], while 1-substituted 4-acetyl-3-hydroxyspiro[2,5-dihydropyrrole-5,3'-indole]-2,2'-diones are obtained by the reaction of methyl acetylpyruvate, isatin, and methylamine (tryptamine) [3].

We found that adducts of 3'-aroyl-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-diones with tetramethylguanidine **1a**,**b** are formed when equimolar amounts of methyl aroylpyruvates, isatin, and N,N,N',N'-tetramethylguanidine are briefly heated in dioxane. Treatment of the adducts with dilute hydrochloric acid at room temperature gave 3'-aroyl-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-diones **2a**,**b**.

The obtained compounds **1** and **2** are colorless crystalline substances readily soluble in DMSO, DMF, alcohol, and acetone and insoluble in chloroform and water.

The IR spectra of compounds **1a**,**b** contain bands for the stretching vibrations of the carbonyl in the side chain (1672-1736), the carbonyl group of the isatylidene radical (1724-1736), the lactone carbonyl group (1768-1772), the enolic hydroxyl group (3160), and the NH bonds (at 3312 and 3328 cm^{-1} respectively).

The ^1H NMR spectra of compounds **1a**,**b** contain signals for the 12 protons of the four methyl groups of tetramethylguanidine in the form of a singlet at 2.87-2.88, multiplets for the aromatic protons at 6.82-8.04, singlets for the two protons of the NH and HO groups at 7.68 and 7.76, and singlets for the proton of the NH group at 10.34 and 10.37 ppm.

The IR spectra of compounds **2a**,**b** contain bands for the stretching vibrations of the carbonyl group in the side chain (1688), the carbonyl group of the isatylidene radical (1716), the lactone carbonyl group (1788-1792), the enolic hydroxyl group, and the NH bonds at 3288 and 3296 cm^{-1}.

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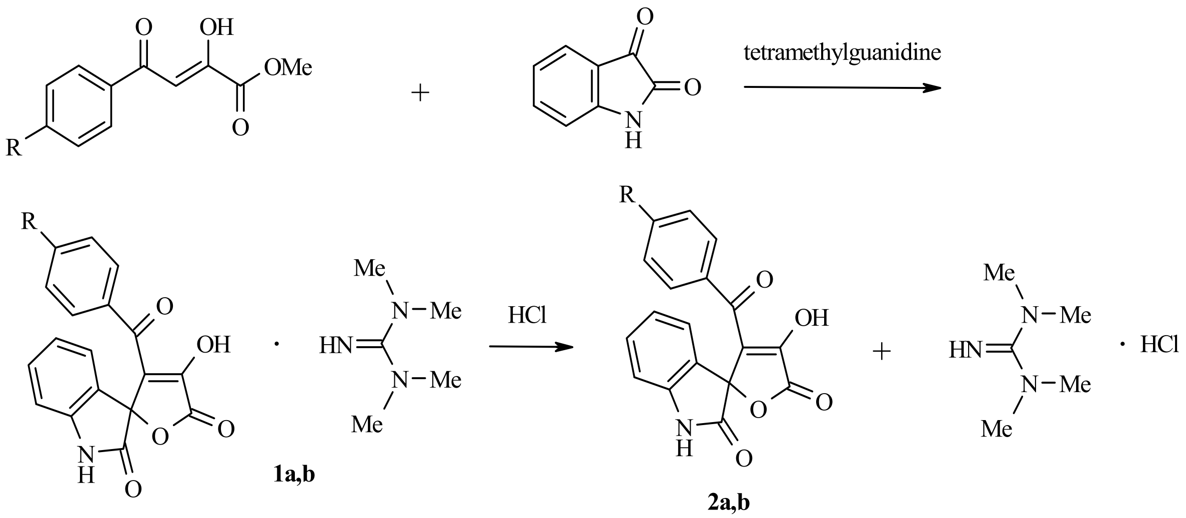

Unlike the ^{1}H NMR spectra of the adducts **1a**,**b** the ^{1}H NMR spectra of compounds **2a**,**b** do not contain signals for the protons of tetramethylguanidine and the HO and NH= groups, but there is a downfield shift of the signal for the proton of the NH group in the isatylidene fragment: 10.90 and 10.92 ppm respectively.

The structures are confirmed by the presence of the peaks of fragment ions in the mass spectra of compounds **1a** and **2a**,**b**.

EXPERIMENTAL

The IR spectra were obtained in vaseline oil on a Specord M-89 instrument. The ^{1}H NMR spectra were obtained in DMSO-d$_6$ on a Bruker DRX 500 spectrometer (500 MHz) with TMS as internal standard. The mass spectra were obtained on a Finnigan MAT Incos 50 instrument at 70 eV.

Adduct of 4'-Hydroxy-3'-(4-methylbenzoyl)spiro[indole-3,2'-furan]-2,5'(1H)-dione with Tetramethylguanidine (1a). A mixture of methyl 4-methylbenzoylpyruvate (4.40 g, 0.02 mol) and isatin (2.94 g, 0.02 mol) in dioxane (10 ml) was heated until dissolved, and tetramethylguanidine (2.53 ml, 0.02 mol) was added to the solution cooled to room temperature. The reaction mixture was kept at 20°C for 24 h. The precipitate was filtered off and recrystallized from 2-propanol. The yield was 6.60 g (73%); mp 144-146°C (isopropyl alcohol). IR spectrum, ν, cm^{-1}: 1676 (CO), 1724 (NCO), 1768 (COO), 3160 (HO), 3328 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.31 (3H, s, CH$_3$); 2.87 (12H, s, 4CH$_3$); 6.82 (1H, d, *J* = 7.7, H-4); 6.85 (1H, t, *J* = 7.7, H-5); 7.03 (1H, d, *J* = 7.7, H-7); 7.12 (2H, d, *J* = 8.1, H-3,5, $C_6\underline{H}_4CH_3$); 7.18 (1H, t, *J* = 7.7, H-6); 7.68 (2H, s, NH$_2$); 7.85 (2H, d, *J* = 8.1, H-2,6, $C_6\underline{H}_4CH_3$); 10.34 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 291 $[M-CO_2]^+$ (2.10), 119 $[M-COC_6H_4CH_3]^+$ (58.56), 115 $[C_5H_{13}N_3]^+$ (17.52), 44 $[CO_2]^+$ (100). Found, %: C 63.85; H 5.85; N 12.52. $C_{19}H_{13}NO_5 \cdot C_5H_{13}N_3$. Calculated, %: C 63.99; H 5.82; N 12.44.

Adduct of 3'-(4-Fluorobenzoyl)-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-dione with Tetramethylguanidine (1b). This compound was obtained similarly. The yield was 6.20 g (68%); mp 134-136°C (2-propanol). IR spectrum, ν, cm^{-1}: 1672 (CO), 1736 (NCO), 1772 (COO), 3160 (HO), 3312 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.88 (12H, s, 4CH$_3$); 6.82 (1H, d, *J* = 7.5, H-4); 6.86 (1H, t, *J* = 7.5, H-5); 7.04 (1H, d, *J* = 7.5, H-7); 7.12 (2H, t, *J* = 8.9, H-3,5, $C_6\underline{H}_4F$); 7.20 (1H, t, *J* = 7.5, H-6); 7.76 (2H, s, NH$_2$); 8.04 (2H, t, *J* = 8.9, H-2,6, $C_6\underline{H}_4F$); 10.37 (1H, s, NH). Found, %: 60.98; H 5.07; F 4.06; N 12.40. $C_{18}H_{10}FNO_5 \cdot C_5H_{13}N_3$. Calculated, %: C 60.79; H 5.10; F 4.18; N 12.33.

4'-Hydroxy-3'-(4-methylbenzoyl)spiro[indole-3,2'-furan]-2,5'(1H)-dione (2a). The adduct of compound **1a** was treated with a solution of 8.3% HCl at room temperature, and the precipitate was filtered off and recrystallized from alcohol. The yield was 5.65 g (84%); mp 211-213°C (alcohol). IR spectrum, ν, cm^{-1}: 1688 (CO), 1716 (NCO), 1792 (COO), 3288 (HO, NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 6.91 (1H, d, *J* = 7.55, H-4); 6.93 (1H, t, *J* = 7.55, H-5); 7.29 (2H, d, *J* = 8.2, H-3,5, $C_6\underline{H}_4CH_3$); 7.31 (1H, t, *J* = 7.55, H-6'); 7.50 (1H, d, *J* = 7.55, H-7'); 7.74 (2H, d, *J* = 8.2, H-2,6, $C_6\underline{H}_4CH_3$); 10.90 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 291 $[M-CO_2]^+$ (5.01), 119 $[M-COC_6H_4CH_3]^+$ (73.17), 44 $[CO_2]^+$ (100). Found, %: C 68.20; H 3.88; N 4.26. $C_{19}H_{13}NO_5$. Calculated, %: C 68.06; H 3.91; N 4.18.

3'-(4-Fluorobenzoyl)-4'-hydroxyspiro[indole-3,2'-furan]-2,5'(1H)-dione (2b). This compound was obtained similarly with a yield of 5.40 g (79%); mp 207-209°C (alcohol). IR spectrum, ν, cm^{-1}: 1688 (CO), 1716 (NCO), 1788 (COO), 3296 (HO, NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.93 (1H, d, *J* = 7.3, H-4); 6.96 (1H, t, *J* = 7.3, H-5); 7.30 (1H, t, *J* = 7.3, H-6); 7.34 (2H, d, *J* = 8.85, H-2,6, $C_6\underline{H}_4F$); 7.53 (1H, d, *J* = 7.3, H-7); 7.94 (2H, d, *J* = 8.85, H-3,5, $C_6\underline{H}_4F$); 10.92 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 339 $[M]^+$ (2.30), 295 $[M-CO_2]^+$ (32.53), 146 $[C_7H_5NO]^+$ (33.63), 123 $[COC_6H_4F]^+$ (100), 44 $[CO_2]^+$ (43.24). Found, %: C 63.68; H 2.93; F 5.56; N 4.09. $C_{18}H_{10}FNO_5$. Calculated, %: C 63.72; H 2.97; F 5.60; N 4.13.

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