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Five-Membered 2,3-Dioxo Heterocycles: LIII.* Reaction of 3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with Substituted 1,3,3-Trimethyl-3,4-dihydroisoquinolines. A New Approach to 13-Aza Analogs of Steroids

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Abstract—3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones reacted with substituted 1,3,3-trimethyl-3,4-dihydroisoquinolines to give the corresponding 3-aroyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-diones. 7′,8′-Benzo derivatives of the latter may be regarded as 13-azagonane analogs having a spiro-fused pyrrole ring at C^{16}.

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Recyclizations and heterocyclizations of 4-acyl-1*H*-pyrrole-2,3-diones, including those fused at the *a* side to a heteroring, in reactions with mono- and difunctional nucleophiles provide convenient routes to difficultly accessible fused and bridged aza heterocycles and spiro heterocyclic systems [2, 3]. We previously showed that 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones [4] react with cyclic enamines (N-substituted or unsubstituted 3-amino-5,5-dimethylcyclohex-2-en-1-ones) as 1,3-C,N-binucleophiles via successive attack by the β-CH and NH groups of the enamine on the C^{3a} and C^4 atoms of pyrrolobenzoxazine, respectively. The reaction is accompanied by cleavage of the 1,4-oxazine ring at the C^4–O bond to give the corresponding 3′-aroyl-4′-hydroxy-1′-(*o*-hydroxyphenyl)-6,6-dimethyl-6,7-dihydrospiro[indole-3,2′-pyrrole]-2,4,5′(1*H*,1′*H*,5*H*)-triones [5].

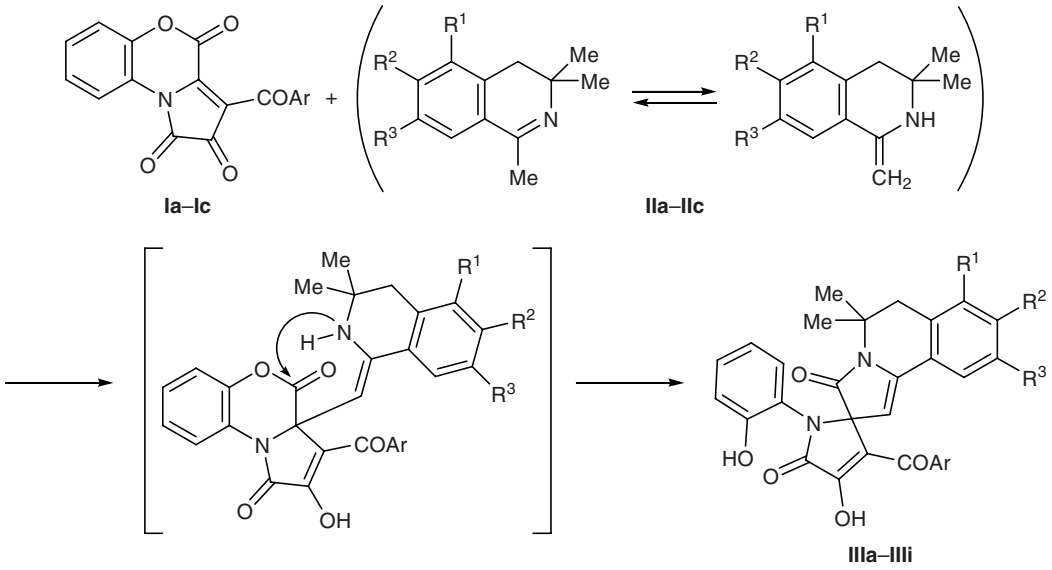
In continuation of our studies on nucleophilic recyclizations of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones we examined reactions of compounds **Ia**–**Ic** with substituted 1,3,3-trimethyl-3,4-dihydroisoquinolines **IIa**–**IIc** which can be regarded as potential 1,3-C,N-binucleophiles. 1,3,3-Trimethyl-3,4-dihydroisoquinolines may be represented as tautomeric 3,3-dimethyl-1-methylidene-1,2,3,4-tetrahydroisoquinolines possessing an enamine moiety with two approximately equally nucleophilic groups. These tautomers can react with strongly electrophilic 2,3-dioxo heterocycles at both NH [6] and β-CH nucleophilic centers [7]. The direction of initial nucleophilic attack by one of the above groups on one among possible electrophilic centers in **Ia**–**Ic** (C^1, C^2, C^{3a}, or C^4) could determine the structure of the final products.

By heating equimolar mixtures of pyrrolobenzoxazinetriones **Ia**–**Ic** with isoquinolines **IIa**–**IIc** in boiling anhydrous benzene over a period of 1–1.5 min we isolated in high yields the corresponding 3-aroyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-diones **IIIa**–**IIIi** [8] (Scheme 1). Compounds **IIIa**–**IIIi** are colorless or light yellow crystalline substances which melt with decomposition at high temperature; they are readily soluble in DMF and DMSO, poorly soluble in other common organic solvents, and insoluble in saturated hydrocarbons and water. Compounds **IIIa**–**IIIi** showed a positive test (cherry color) for enolic or phenolic hydroxy group on treatment with an alcoholic solution of iron(III) chloride.

In the IR spectra of **IIIa**–**IIIi** we observed a broad absorption band at 3200–3280 cm^{-1} due to stretching vibrations of the OH groups and carbonyl absorption bands at 1692–1720 (one or two peaks, lactam carbon-

* For communication LII, see [1].

Scheme 1.



I, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**); **II**, $R^1 = R^2 = R^3 = H$ (**a**); $R^1 = H$, $R^2 = R^3 = MeO$ (**b**); R^1R^2 = benzo[*f*], $R^3 = H$ (**c**); **III**, $R^1 = R^2 = R^3 = H$, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**); $R^1 = H$, $R^2 = R^3 = MeO$, Ar = Ph (**d**), 4-$MeOC_6H_4$ (**e**), 4-BrC_6H_4 (**f**); R^1R^2 = benzo[*f*], $R^3 = H$, Ar = Ph (**g**), 4-$MeOC_6H_4$ (**h**), 4-BrC_6H_4 (**i**).

yl groups) and 1620–1645 cm^{-1} (aroyl carbonyl). The ^1H NMR spectra of compounds **IIIa**–**IIIi** in DMSO-d_6 contained signals from protons in the aromatic rings and substituents attached thereto, two singlets at δ 1.29–1.49 (**IIIa**–**IIIf**) or 1.46–1.58 ppm (**IIIg**–**IIIi**) from the methyl groups in the isoquinoline fragment, a doublet of doublets at δ 2.62–2.82 (**IIIa**–**IIIf**) or 2.99–3.33 ppm (**IIIg**–**IIIi**) from diastereotopic protons on $C^{6'}$, a singlet at δ 5.54–5.72 (**IIIa**–**IIIf**) or 5.81–5.83 ppm (**IIIg**–**IIIi**) from the vinylic proton on $C^{1'}$, a singlet at δ 9.19–9.72 ppm from the phenolic hydroxy proton, and a broadened singlet at δ 11.92–12.46 ppm from the enolic hydroxy group. It is seen that fusion of a benzene ring at the *f* side of the isoquinoline ring (compounds **IIIg**–**IIIi**) leads to an appreciable downfield shift of signals from the methyl, methylene, and vinyl protons in the pyrroloisoquinoline fragment relative to the corresponding signals of compounds **IIIa**–**IIIf**. The spectral parameters of spiro compounds **IIIa**–**IIIi** are similar to those of structurally related substituted spiro[indole-3,2′-pyrroles] and spiro[benzo[*h*]pyrrolo[2,1-*a*]isoquinoline-2,2′-pyrroles whose structure was proved by X-ray analysis [5, 9].

Presumably, the first stage of the process is addition of the activated β-CH group of the enamine tautomer of **II** to the C^{3a} atom of pyrrolobenzoxazinetrione **I**. The subsequent intramolecular attack by the isoquinoline nitrogen atom on the lactone carbonyl carbon atom in the benzoxazine ring leads to closure of pyrrole ring and cleavage of the oxazine ring at the C^4–O bond.

It should be noted that 7′,8′-benzo-fused spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-diones **IIIg**–**IIIi** may be regarded as analogs of 13-azagonane having a spiro-fused pyrrole ring at C^{16} of the steroid skeleton; therefore, the described reaction opens a new route to such compounds.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker AM-400 instrument (400 MHz for ^1H) relative to tetramethylsilane as internal reference. The purity of the isolated compounds was checked by thin-layer chromatography on Silufol plates using ethyl acetate or ethyl acetate–benzene (1:5) as eluent; the chromatograms were developed by treatment with iodine vapor.

3-Benzoyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIIa). A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of isoquinoline **IIa** in 10 ml of anhydrous benzene was heated for 3 min under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 72%,

mp 215–216°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3230 br (OH); 1720, 1709 ($C^{3'}$=O, C^{5}=O); 1630 (PhC=O). ^{1}H NMR spectrum, δ, ppm: 1.41 s (3H, Me), 1.49 s (3H, Me), 2.62 d.d and 2.82 d.d (1H each, 6′-H, *J* = 15.9 Hz), 5.72 s (1H, 1′-H), 6.75–7.77 m (13H, H_{arom}), 9.67 s (1H, 2″-OH), 12.20 br.s (1H, 4-OH). Found, %: C 73.14; H 4.81; N 5.64. $C_{30}H_{24}N_2O_5$. Calculated, %: C 73.16; H 4.91; N 5.69.

Compounds **IIIb–IIIi** were synthesized in a similar way.

4-Hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxybenzoyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIIb). Yield 77%, mp 211–213°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3200 br (OH); 1705 ($C^{3'}$=O, C^{5}=O); 1630 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.38 s (3H, Me), 1.49 s (3H, Me), 2.62 d.d and 2.81 d.d (1H each, 6′-H, *J* = 15.9 Hz), 3.85 s (3H, OMe), 5.68 s (1H, 1′-H), 6.73–7.79 m (12H, H_{arom}), 9.62 s (1H, 2″-OH), 12.00 br.s (1H, 4-OH). ^{13}C NMR spectrum, δ_C, ppm: 25.47 and 26.37 (5′-CH_3), 43.22 ($C^{6'}$), 53.57 ($C^{5'}$), 55.45 (MeO), 72.52 (C_{spiro}), 97.16 ($C^{1'}$), 113.41–132.62 m (C_{arom}), 142.85 ($C^{10b'}$), 151.37 (COH), 154.54 (C^{5}), 162.92 (C^{4}), 165.48 (**C**OMe), 174.15 ($C^{3'}$), 186.93 (**C**OAr). Found, %: C 71.24; H 5.07; N 5.34. $C_{31}H_{26}N_2O_6$. Calculated, %: C 71.25; H 5.02; N 5.36.

3-(4-Bromobenzoyl)-4-hydroxy-1-(2-hydroxyphenyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIIc). Yield 87%, mp 224–225°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3210 br (OH); 1705, 1690 ($C^{3'}$=O, C^{5}=O); 1635 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.40 s (3H, Me), 1.47 s (3H, Me), 2.62 d.d and 2.82 d.d (1H each, 6′-H, *J* = 15.9 Hz), 5.70 s (1H, 1′-H), 6.74–7.73 m (12H, H_{arom}), 9.64 s (1H, 2″-OH), 12.40 br.s (1H, 4-OH). Found, %: C 63.06; H 4.06; Br 13.98; N 4.90. $C_{30}H_{23}BrN_2O_5$. Calculated, %: C 63.05; H 4.05; Br 13.97; N 4.92.

3-Benzoyl-4-hydroxy-1-(2-hydroxyphenyl)-8′,9′-dimethoxy-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIId). Yield 91%, mp 160–161°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3210 br (OH); 1712, 1705 ($C^{3'}$=O, C^{5}=O); 1625 (PhC=O). ^{1}H NMR spectrum, δ, ppm: 1.29 s (3H, Me), 1.43 s (3H, Me), 2.50 d.d and 2.67 d.d (1H each, 6′-H, *J* = 15.9 Hz), 3.84 s (3H, OMe), 3.88 s (3H, OMe), 5.57 s (1H, 1′-H), 6.68–7.79 m (11H, H_{arom}, 7′-H, 10′-H), 9.30 s (1H, 2″-OH), 12.25 br.s (1H, 4-OH). Found, %: C 69.55; H 4.11; N 5.07. $C_{32}H_{28}N_2O_7$. Calculated, %: C 69.50; H 4.16; N 5.06.

4-Hydroxy-1-(2-hydroxyphenyl)-8′,9′-dimethoxy-3-(4-methoxybenzoyl)-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIIe). Yield 93%, mp 217–218°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3205 br (OH); 1719, 1707 ($C^{3'}$=O, C^{5}=O); 1630 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.44 s (3H, Me), 1.47 s (3H, Me), 2.52 d.d and 2.72 d.d (1H each, 6′-H, *J* = 15.9 Hz), 3.69 s (3H, OMe), 3.73 s (3H, OMe), 3.84 s (3H, OMe), 5.56 s (1H, 1′-H), 6.73–7.79 m (10H, H_{arom}, 7′-H, 10′-H), 9.64 s (1H, 2″-OH), 11.92 br.s (1H, 4-OH). Found, %: C 68.03; H 5.19; N 4.81. $C_{33}H_{30}N_2O_8$. Calculated, %: C 68.02; H 5.18; N 4.83.

3-(4-Bromobenzoyl)-4-hydroxy-1-(2-hydroxyphenyl)-8′,9′-dimethoxy-5′,5′-dimethyl-5′,6′-dihydro-1*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*a*]isoquinoline]-3′,5-dione (IIIf). Yield 89%, mp 181–182°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3205 br (OH); 1710 ($C^{3'}$=O, C^{5}=O); 1620 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s (3H, Me), 1.41 s (3H, Me), 2.48 d.d and 2.66 d.d (1H each, *J* = 15.9 Hz), 3.85 s (3H, OMe), 3.89 s (3H, OMe), 5.54 s (1H, 1′-H), 6.67–7.72 m (10H, H_{arom}, 7′-H, 10′-H), 9.19 s (1H, 2″-OH), 12.30 br.s (1H, 4-OH). Found, %: C 60.86; H 4.31; Br 12.05; N 4.44. $C_{32}H_{27}BrN_2O_7$. Calculated, %: C 60.85; H 4.32; Br 12.06; N 4.43.

3′-Benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-5,6-dihydro-1′*H*-spiro[benzo[*f*]pyrrolo-[2,1-*a*]isoquinoline-9,2′-pyrrole]-5′,8-dione (IIIg). Yield 90%, mp 209–211°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3200 br (OH); 1703, 1695 ($C^{5'}$=O, C^{8}=O); 1633 (PhC=O). ^{1}H NMR spectrum, δ, ppm: 1.48 s (3H, Me), 1.57 s (3H, Me), 2.99 d.d and 3.32 d.d (1H each, 5-H, *J* = 16.5 Hz), 5.83 s (1H, 10-H), 6.73–8.12 m (15H, H_{arom}, 1-H, 2-H, 3-H, 4-H, 11-H, 12-H), 9.65 s (1H, 2″-OH), 12.26 br.s (1H, 4′-OH). Found, %: C 75.26; H 4.83; N 5.16. $C_{34}H_{26}N_2O_5$. Calculated, %: C 75.25; H 4.84; N 5.15.

4′-Hydroxy-1′-(2-hydroxyphenyl)-3′-(4-methoxybenzoyl)-6,6-dimethyl-5,6-dihydro-1′*H*-spiro[benzo-[*f*]pyrrolo[2,1-*a*]isoquinoline-9,2′-pyrrole]-5′,8-dione (IIIh). Yield 93%, mp 235–237°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3280 br (OH), 1700 ($C^{5'}$=O, C^{8}=O), 1625 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.46 s (3H, Me), 1.58 s (3H, Me), 3.01 d.d and 3.31 d.d (1H each, 5-H, *J* = 16.4 Hz), 3.85 s (3H, OMe), 5.81 s (1H, 10-H), 6.73–8.12 m (14H, H_{arom},

1-H, 2-H, 3-H, 4-H, 11-H, 12-H), 9.65 s (1H, 2″-OH), 12.02 br.s (1H, 4-OH). Found, %: C 73.41; H 4.93; N 4.89. $C_{35}H_{28}N_2O_6$. Calculated, %: C 73.40; H 4.94; N 4.88.

3′-(4-Bromobenzoyl)-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-5,6-dihydro-1′*H*-spiro[benzo[*f*]pyrrolo[2,1-*a*]isoquinoline-9,2′-pyrrole]-5′,8-dione (IIIi). Yield 89%, mp 216–218°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3240 br (OH); 1706, 1692 ($C^{5'}$=O, C^{8}=O); 1645 (ArC=O). ^{1}H NMR spectrum, δ, ppm: 1.48 s (3H, Me), 1.56 s (3H, Me), 3.00 d.d and 3.33 d.d (1H each, 5-H, J = 16.5 Hz), 5.83 s (1H, 10-H), 6.73–8.12 m (14H, H_{arom}, 1-H, 2-H, 3-H, 4-H, 11-H, 12-H), 9.67 s (1H, 2″-OH), 12.46 br.s (1H, 4′-OH). Found, %: C 65.71; H 4.05; Br 12.80; N 4.51. $C_{34}H_{25}BrN_2O_5$. Calculated, %: C 65.70; H 4.06; Br 12.86; N 4.50.

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