

Heteroannellation of 3,4-dihydroisoquinoline with (3*H*,5*H*)-3-acylthiophene-2,4-diones: one-stage synthesis of new heterocyclic steroid analogues, 8-aza-16-thiagonanes

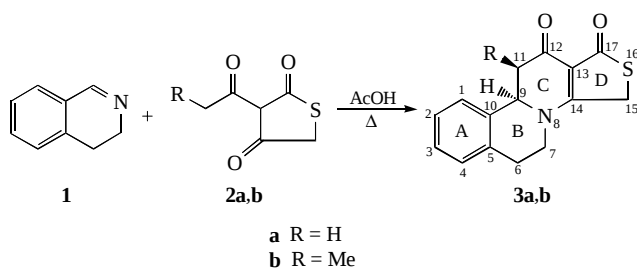
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New 8-aza-16-thiasteroid analogues, benzo[*a*]thieno[*f*]quinolizines, have been synthesised by the [2 + 4]heteroannellation of 3,4-dihydroisoquinoline with 3-acylthiotetronic acids.

Condensed carbocycles and heterocycles are usually prepared by the following two ways: (1) a convergent synthesis which consists in the consecutive addition of rings to a principal carbocyclic or heterocyclic substrate and (2) a block synthesis when previously synthesised molecular units are combined at the final stage.¹ The block strategy is more effective, and a large number of condensed nitrogen-containing heterocycles have been prepared in this manner, namely, benzo[*a*]- and dibenzo[*a,f*]quinolizines,^{2(a)} benzo[*a*]furo[*f*]quinolizines,^{2(b)} benzo[*a*]pyrrolo[*f*]quinolizines,^{2(c)} benzo[*a*]pyrimidino[4,5-*f*]quinolizines^{2(d)} and many others.³ All of the above compounds have been synthesised according to a single classical strategy involving the annellation ([2 + 4]cyclocondensation) reaction of cyclic Schiff's bases, usually 3,4-dihydroisoquinolines, with β -dicarbonyl or β,β' -tricarbonyl compounds and their enol derivatives.^{2,3(b)-(d)}

To prepare new heterocycles, we tried to extend this approach by using 3,4-dihydroisoquinoline **1** and 3-acylthiotetronic acids such as (3*H*,5*H*)-3-acetylthiophene-2,4-dione **2a** and (3*H*,5*H*)-3-propionylthiophene-2,4-dione **2b** in the annellation.⁴ We found that [2 + 4]cyclocondensation takes place when a mixture of compounds **1** and **2a** or **2b** is boiled in glacial acetic acid.[†] The reaction products are new heterocycles, benzo[*a*]thieno[*f*]quinolizines **3a,b**.[‡] Note that contrary to cyclocondensations with the participation of 2-acetylcylohexane-1,3-diones^{2(a),5} and dihydrodehydracetic acid,^{3(a)} which proceed in rather mild conditions, the reaction of **1** with 3-acylthiotetronic acids **2a,b**, similarly to condensations with 2-acetylcyclopentane-1,3-dione⁶ and 3-acetyltetronic^{2(b)} and 3-acetyltetramic^{2(c)} acids, requires prolonged heating (8–15 h). We believe that this feature of β,β' -tricarbonyl compounds with five-membered rings is due to steric hindrances of the attack on a ring carbonyl by nitrogen atoms of Schiff's bases.



Prepared ABCD-tetracyclic 8-aza-16-thiagona-12,17-diones (benzo[*a*]thieno[4,3-*f*]quinolizines) **3a,b**,⁵ as well as all their analogues which can be synthesised by this method, offer promise as biologically active substances and models for studying the structure–activity relationship in immune regulators such as

[†] A mixture of 1.86 g (14.2 mmol) of 3,4-dihydroisoquinoline **1** and 2.24 g (14.2 mmol) of 3-acylthiotetronic acids **2a,b**⁴ in 50 ml of glacial acetic acid was refluxed for 9 h and then allowed to cool to room temperature overnight. The precipitated orange crystals were separated, washed with acetic acid–diethyl ether (1:1), dried and recrystallised from a mixture of acetic and trifluoroacetic acids. Thus, 3.00 g (78.5%) of 8-aza-16-thiagona-1,3,5(10),13-tetraen-12,17-dione **3a** (mp 320 °C, decomp.) and 3.01 g (75.6%) of 11-methyl-8-aza-16-thiagona-1,3,5(10),13-tetraen-12,17-dione **3b** (mp 288–297 °C, decomp.) were obtained.

condensed dibenzo[*a,f*]- and benzo[*a*]hetareno[*f*]quinolizine derivatives.⁷

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[‡] For **3a**: ¹H NMR (200 MHz, CDCl₃, TMS) δ : 3.15 [t, 1H, C(11)H_B, *J* 18.0 Hz], 3.22 [ttt, 1H, C(6)H_A, *J* 11.0, 13.0, 3.0 Hz], 3.29 [mmm, 1H, C(6)H_A, *J* 13.0, 3.0, 3.0 Hz], 3.45 [dd, 1H, C(11)H_A, *J* 18.0, 5.0 Hz], 3.88 [ttt, 1H, C(7)H_A, *J* 13.0, 11.0, 3.0 Hz], 4.34 [mmm, 1H, C(7)H_A, *J* 13.0, 3.0, 3.0 Hz], 4.58 [d, 1H, C(15)H_B, *J* 18.5 Hz], 4.68 [d, 1H, C(15)H_A, *J* 18.5 Hz], 5.46 [dd, 1H, C(9)H_X, *J* 18.0, 5.0 Hz], 7.20–7.48 [m, 4H, C(1)H, C(2)H, C(3)H, C(4)H]. ¹³C NMR (90 MHz, CF₃CO₂D, TMS) δ : 30.056, 35.227, 40.850, 49.006, 60.724 (C-9), 109.985 (C-12), 127.263, 130.190, 130.866 $\times$ 2, 132.296, 134.287, 177.985 (C-14), 190.453, 200.015. IR (KBr, ν /cm⁻¹): 3100–2830, 1685 (sh.), 1672, 1608, 1580, 1565–1540, 1473–1445, 1396, 1347, 1320, 1285, 1230, 876, 830, 769. UV [EtOH, $\lambda_{\max}$ /nm (ϵ): 202.4 (36070), 230.0 (11595), 265.0 (13630), 302.4 (12245); $\lambda_{\min}$ /nm (ϵ): 219.1 (10235), 245.9 (6450), 280.0 (8985)]. Found (%): C, 66.24; H, 4.79; N, 5.07; S, 12.12. Calc. for C₁₅H₁₃NO₂S (%): C, 66.40; H, 4.83; N, 5.16; S, 11.82. MS, *m/z*: 271.34. For **3b**: ¹H NMR (200 MHz, CDCl₃, TMS) δ : 0.78 [d, 3H, C(11)Me, *J* 7.0 Hz], 2.74 [m, 1H, C(11)H_B, *J* 4.0, 7.0 Hz], 2.99 [tt, 1H, C(6)H_A, *J* 4.0, 4.0, 12.0 Hz], 3.12 [ddd, 1H, C(6)H_A, *J* 4.0, 12.0, 12.0 Hz], 3.50 [ddd, 1H, C(7)H_A, *J* 4.0, 12.0, 12.0 Hz], 4.04 [d, 1H, C(15)H_B, *J* 18.0 Hz], 4.16 [tt, 1H, C(7)H_A, *J* 4.0, 4.0, 12.0 Hz], 4.24 [d, 1H, C(15)H_A, *J* 18.0 Hz], 5.10 [d, 1H, C(9)H_X, *J* 4.0 Hz], 7.15 [dd, 1H, C(1)H, *J* 2.0, 8.0 Hz], 7.21–7.42 [m, 3H, C(2)H, C(3)H, C(4)H]. IR (KBr, ν /cm⁻¹): 3100–2830, 1698 (sh.), 1630, 1596, 1573, 1560 (sh.), 1500, 1477, 1460 (sh.), 1405, 1380, 1360–1330, 1307, 1292, 1240, 897, 811, 797, 770, 755. UV [EtOH, $\lambda_{\max}$ /nm (ϵ): 264.6 (15860), 303.9 (12950); $\lambda_{\min}$ /nm (ϵ): 238.1 (6290), 281.2 (7280)]. Found (%): C, 67.27; H, 5.14; N, 4.87; S, 11.50. Calc. for C₁₆H₁₅NO₂S (%): C, 67.34; H, 5.30; N, 4.91; S, 11.24. MS, *m/z*: 285.36.

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