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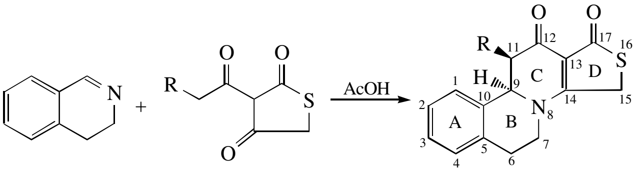
New 8-aza-16-thiasteroid analogues, benzo[*a*]thieno[*f*]quinolizines, have been synthesised by the [2 + 4]heteroannelation of 3,4-dihydroisoquinoline with 3-acylthiotetronic acids.

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 annelation ([2 + 4]cyclocondensation) reaction of cyclic Schiff's bases, usually 3,4-dihydroisoquinolines, with -dicarbonyl or , ′-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 annelation.[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-acetylcyclohexane-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-dione[6] and 3-acetyltetronic[2(*b*)] and 3-acetyltetramic[2(*c*)] acids, requires prolonged heating (8–15 h). We believe that this feature of , ′-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.



1 **2a**,**b** **3a**,**b**

a R = H
b R = Me

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

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[†] 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.

[‡] For **3a**: ^{1}H NMR (200 MHz, $CDCl_3$, 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_e, *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_e, *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]. ^{13}C NMR (90 MHz, CF_3CO_2D, TMS) δ: 30.056, 35.227, 40.850, 49.006, 60.724 (C-9), 109.985 (C-12), 127.263, 130.190, 130.866×2, 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, λ_{max}/nm (ε)]: 202.4 (36070), 230.0 (11595), 265.0 (13630), 302.4 (12245); λ_{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 $C_{15}H_{13}NO_2S$ (%): C, 66.40; H, 4.83; N, 5.16; S, 11.82. MS, *m*/*z*: 271.34.

For **3b**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ: 0.78 [d, 3H, C(11)Me, *J* 7.0 Hz], 2.74 [m, 1H, C(11)H_e, *J* 4.0, 7.0 Hz], 2.99 [tt, 1H, C(6)H_e, *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_e, *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_a, *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, λ_{max}/nm (ε)]: 264.6 (15860), 303.9 (12950); λ_{min}/nm (ε): 238.1 (6290), 281.2 (7280). Found (%): C, 67.27; H, 5.14; N, 4.87; S, 11.50. Calc. for $C_{16}H_{15}NO_2S$ (%): C, 67.34; H, 5.30; N, 4.91; S, 11.24. MS, *m*/*z*: 285.36.

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