SYNTHESIS AND PROPERTIES OF $C_{(9)}$ AND $C_{(11)}$ ETHYL DERIVATIVES OF 8-AZA-D-HOMOGONANES. THE STERIC FACTOR IN THE ANNELATION OF CYCLIC SCHIFF BASES BY β-TRIKETONES

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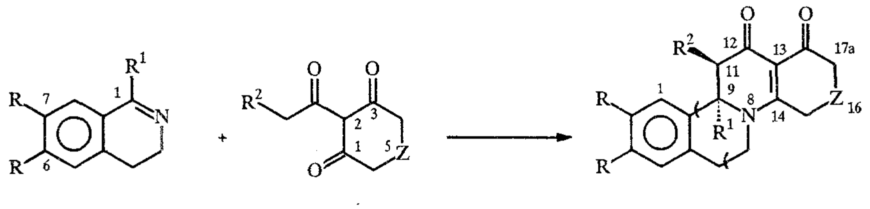
We have studied the steric factors due to the substituents at $C_{(1)}$ *of 3,4-dihydroisoquinolines and in the acyl segment of 2-acyl-1,3-cyclohexanediones that affect the annelation of cyclic Schiff bases by β-triketones. Ethyl substituents at* $C_{(1)}$ *of 3,4-dihydroisoquinolines show about twice as much retarding effect on reaction rate and yield of desired products as does the replacement of acetyl by butanoyl in 2-acyl-1,3-cyclohexanediones. Derivatives that are ethylated at* $C_{(11)}$ *of aza-D-homogona-1,3,5(10),13-tetraen-12,17a-diones exist as a mixture of conformers hindered at the C ring.*

We have previously shown that in the annelation of cyclic Schiff bases by 2-acyl-1,3-cycloalkanediones, in addition to the 3,4-dihydroisoquinolines unsubstituted at $C_{(1)}$ [1, 2], those that are alkyl-substituted at $C_{(1)}$ also react [3, 4] to form derivatives that are angularly alkylated at $C_{(9)}$. It was also shown that not only do the 2-acetyl compounds react, but also homologous acyl derivatives of 1,3-cycloalkanediones [4, 5]. The products are 8-azasteroids alkylated at $C_{(11)}$, that belong to a new class of low-molecular-weight immunomodulators. However, from the above data it was not possible to evaluate the role of the steric factor in annulation. In order to answer this question and to determine the effect of substituents at $C_{(9)}$ and $C_{(11)}$ of 8-azasteroids on the direction and level of the resulting immunotensive action, we have synthesized and studied some properties of $C_{(9)}$ and $C_{(11)}$ ethyl derivatives of this series.

As starting Schiff bases we used 3,4-dihydroisoquinolines, both unsubstituted and ethyl-substituted at $C_{(1)}$ (Ia-d). These were synthesized by the Bischler—Napralski reaction from the respective amines: from phenethylamine derivatives by the action of polyphosphoric acid (Ia, b), and from 3,4-dimethoxyphenylethylamine by the action of phosphorus oxychloride (Ic, d) [6]. The 2-acyl-1,3-cyclohexanediones (IIa-d) were synthesized by Claisen—Haas isomerization of the enol acylates of 1,3-cyclohexanediones by the action of aluminum chloride or 4-dimethylaminopyridine [7, 8]. The structures of Ia-d and IIa-d were confirmed by their physicochemical properties and by comparison with published data.

Scheme 1



Ia-d IIa-d IIIa-h

Ia,b, IIIa, a,c,e,g,h, R = H; Ic,d, IIIb,d,f R = OMe; Ia,cIIIa-d R^1 = H; Ib,dIII e-h R^1 = Et; IIa,b
IIIe,g R^2 = H; IIc,d, IIIa-d,h R^2 = Et; IIa,c, IIIa,b,d,f,h Z = CH_2; IIb,d, IIIc,d,g Z = CMe_2

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The reaction of compounds Ia-d with compounds IIa-d, which forms azasteroids IIIa-h (Scheme 1), was carried out by boiling an equimolar mixture of the reagents in ethanol.

Analysis of reaction times and yields of compounds III (see Experimental) show convincingly that ethyl substituents at $C_{(1)}$ of compounds Ib-d affect reaction rate and yield of annelation product substantially more than do 2-butanoyl substituents in compounds IIc-d. Compounds IIIe-g were obtained in yields up to 59% after 20-40 h boiling in alcohol, whereas the 9-11 diethyl compounds IIIa-d were obtained in 75-90% yield after 3-5 h boiling: the 9-11 diethyl compound IIIh was obtained in only 15.5% yield after 50 h boiling. There was no substantial effect of substituents in the aromatic ring of Ia-d, nor was there any effect of substituents at $C_{(5)}$ of the β-triketones IIb, d on reaction rate or yield of 8-aza-D-homogonanes. It is interesting that dimethoxy compounds IIIb, d, f have melting points about 80°C higher than the demethoxy analogs IIIa-c, e, g, h. This is probably due to the lower polarity of the latter, and affects the lipophilic factor at the level of physiological activity.

The IR spectra of the 8-aza-D-homogonanes IIIa-h, as those of the previously described compounds of this series [1-5], show a typical collection of absorption bands in the 1700-1400 cm^{-1} region; they show the presence of α-acyl-β-aminovinylcarbonyl segments, viz., $N_{(8)}—C_{(14)}=C_{(13)}(—C_{(12)}=O)—C_{(17a)}=O$. But a rigorous assignment of these bands is troublesome. The bands at 1690-1670 cm^{-1} are an exception; they are typical of the stretching vibrations of the α-acylcarbonyl group [10]. Here it remains uncertain to which of the carbonyls (at C_{12} or C_{17a}) it belongs. According to the concept previously expressed by us [11, 12] concerning "mesomeric tautomerism" in this series of compounds, this band is due to contributions by both $C_{(12)}=O$ and $C_{(17a)}=O$. We should also notice the splitting of this band for compound IIIh, observed in this series for the first time, that indicates a complex structure. The assignment of the other bands in this region is a problem to which a separate article will be devoted.

The electron spectra of compounds IIIa-h contain two broad intense bands, at 265-267 nm (band half-width ~30 nm) and 300-311 nm (band half-width ~50 nm); these are typical of 8-aza-steroids that contain an α-acyl-β-aminovinylcarbonyl segment, and correspond to the chromophores of that segment. The lower frequency band at 300-311 nm belongs to the $\pi—\pi^*$ electron transition of the β-aminovinylcarbonyl chromophore, while the higher frequency band at 265-267 nm belongs to the same transitions of the α-acyl group that is conjugated with it. Here the question arises, which grouping, $N_{(8)}—C_{(14)}=C_{(13)}—C_{(12)}=O$ or $N_{(8)}—C_{(14)}=C_{(13)}—C_{(17a)}=O$ should be assigned to the β-aminovinylcarbonyl (at 300-311 nm), and which of the carbonyl groups ($C_{(12)}=O$ or $C_{(17a)}=O$) should be assigned to the conjugated α-acyl segment. The question is answered from the viewpoint of the same phenomenon, viz., mesomeric tautomerism [11].

A distinctive feature of the PMR spectra of compounds IIIa-h is the presence of ethyl signals; these appear as triplets for methyl groups at 0.76-0.79 ppm for the 11-ethyl derivatives IIIa-d, at 0.83-0.87 ppm for the 9-ethyl derivatives IIIe-g, and as multiplets in the 1.00-1.36 ppm region for IIIa-d and 1.92-2.27 ppm for IIIe-g for methylene groups. It is noteworthy that $\Delta\delta$ for these signals is 0.07 ppm for methyl groups and 0.92 ppm for methylene groups. This shows a significant role for anisotropic factors in determining the location of these signals. In the case of the 9-ethyl derivatives IIIe-g, the spectra lack the resonance signals of the benzyl protons at $C_{(9)}$ (4.7-5.0 ppm); while the signals of the methylene protons at $C_{(11)}$ appear as an AB-spin system but not an ABX spin system. The latter was typical of previously described azasteroid derivatives that were unsubstituted at $C_{(9)}$ and $C_{(11)}$ [1, 2]. The PMR spectra of the 9-ethyl derivatives IIIe-h contain only one set of resonance signals. At the same time the 11-ethyl derivatives IIIa-d show additional signals, specifically for the methyl groups of the ethyl substituents at 1.03-1.08 ppm, and for the $C_{(9)}$ benzyl protons at 4.63-4.68 ppm (see Table 1). It should be noted that according to chromatography these derivatives are homogeneous, and the additional $C_{(9)}—H$ signals have the same SSCC (ΔJ = 1.0-1.5 Hz) as the fundamental signals. The absence of differences between the SSCC of the benzyl protons at $C_{(9)}$ and the proton at $C_{(11)}$ indicates that here we are dealing not with a mixture of cis—trans isomers at $C_{(9)}$ and $C_{(11)}$ [13], but with a mixture of conformers that are hindered in a C ring. These latter can easily be combined into a single thermodynamically preferred conformer by holding their solution with a catalytic amount of acid. It is known that in the presence of up to 1 equivalent of acid stereoisomerization at $C_{(11)}$ is not possible, because an enol immonium derivative is obtained. This in turn is a mixture of tautomers (IV, Scheme 2). Nevertheless this phenomenon facilitates the conformational transitions that lead to the preferred conformer (δ = 4.91-5.0 ppm). On the basis of molecular models and a comparison of the proton SSCC at $C_{(9)}$ and $C_{(11)}$, a structure with a $C_{(12)}=O$ carbonyl lying in front of the plane of the figure, (A), has been assigned to the preferred conformer, while the less-preferred conformer (δ = 4.64-4.68 ppm) is placed behind the plane of the figure, (B), with an α-configuration of the $C_{(9)}$ benzyl proton.

In spite of the $C_{(11)}—C_2H_5$ group, the PMR spectrum of the diethyl derivative IIIh shows only one set of proton resonance signals; this is probably due to the steric effect of the $C_{(9)}—C_2H_5$ group.

Thus our data are evidence for the substantial role of the steric factor in the annelation of cyclic Schiff bases by β-triketones, and they determine some limits to the applicability of the reaction. On the other hand, the signals in the PMR spectra of the

TABLE 1. Spectral Properties of 8-Aza-D-Homogonanes IIIa-h

Compound	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm; SSCC (J, Hz)
1	2	3	4
IIIa	1674, 1607, 1512, 1505, 1494, 1452	200(4,21), 266(4,15), 307(4,18)	0,76 (3H,t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 1,13 (1H,m, $C_{(11)}\underline{CH_2}CH_3$); 1,31 (1Hm., $C_{(11)}\underline{CH_2}CH_3$), 1,92...2,12 (2H, m, $C_{(16)}H_2$); 2,26...2,59 (4H,m, $C_{(15)}H_2$, $C_{(17)}H_2$); 2,59...2,72 (1H,m, $C_{(11)}H$); 2,93 (1H,tt, $C_{(6)}H_e$; 16,8, 3,0, 3,0); 3,06 (1H, dtd., $C_{(6)}H_a$; 16,8, 12,0, 3,0); 3,32 (1H, ddd. $C_{(7)}H_a$; 13,5, 12,0, 3,0); 4,27 (1H,tt, $C_{(7)}H_e$; 13,5, 3,0, 3,0); 5,00 (1H,t., $C_{(9)}H$; 1,8); 7,13...7,33 (4H, arom. m)
IIIa* (~10%)			4,68 (d, $C_{(9)}H$; 3,6); 1,03 (t, $C_{(11)}CH_2\underline{CH_3}$; 7,2)
III b	1677, 1610, 1515...1505, 1450, 1358, 1348, 1325, 1258, 1221, 1125	204(4,62), 235(3,99), 167(4,23), 295 sh(4,23), 306(4,23)	0,78 (3H,t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 1,13...1,28 (2H,m, $C_{(11)}\underline{CH_2}CH_3$); 1,94...2,15 (2H,m, $C_{(16)}H_2$); 2,36...2,55 (3H, m, $C_{(11)}H$, $C_{(15)}H_2$); 2,69...3,06 (4H,m, $C_{(6)}H_a$, $C_{(6)}H_e$ $C_{(17)}H_2$); 3,35 (1H, ddd, $C_{(7)}H_a$; 13,2, 13,2, 3,0); 3,85 (3H, s, OCH₃); 3,88 (3H,s. OCH₃); 4,31 (1H, tt $C_{(7)}H_e$; 13,2, 3,0, 3,0); 4,93 (1H,s $C_{(9)}H$; 1,8); 6,62 (1H, arom.m.; 6,67 (1H, arom.m.)
IIIb* (~40%)			1,04 (t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 4,63 (d, $C_{(9)}H$; 2,4)
IIIc	1675, 1620, 1605, 1515, 1505, 1494, 1452, 1442, 1350, 1332	200(4,28), 266(4,19), 309(4,26)	0,79 (3H,t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 1,12 (3H,s, $C_{(16)}CH_3$); 1,13 (3H,s, $C_{(16)}CH_3$; 1,14...1,36 (2H,m, $C_{(11)}\underline{CH_2}CH_3$); 2,28 (2H,s, $C_{(15)}H_2$); 2,43 (1H, tt, $C_{(11)}H$; 16,0; 7,2; 1,2); 2,52 (1H,d, $C_{(17)}H_B$; 15,6); 2,61 (1H,d, $C_{(17)}H_A$; 15,6); 2,92 (1H,tt, $C_{(6)}H_e$; 16,8, 3,0, 3,0); 3,07 (1H,dtd., $C_{(6)}H_a$; 16,8, 12,0, 3,0); 3,30 (1H,ddd., $C_{(7)}H_a$; 13,2, 12,0, 3,0); 4,27 (1H, tt, $C_{(7)}H_e$; 13,2, 3,0, 3,0); 5,00 (1H, .. $C_{(9)}H$; 1,2); 7,15...7,36 (4H, arom.m.)
IIIc* (~50%)			1,04 (t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 4,67 (d, $C_{(9)}H$; 2,4)
IIId	1680, 1612, 1515, 1503, 1452, 1442, 1347, 1335, 1320, 1257	205(4,60), 234(3,99), 266(4,17), 293 sh(4,19), 308(4,20)	0,79 (3H,t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 1,02...1,32 (2H,m., $C_{(11)}\underline{CH_2}CH_3$); 1,13 (3H,s, $C_{(16)}CH_3$); 1,15 (3H,s, $C_{(16)}CH_3$); 2,30 (2H,s, $C_{(15)}H_2$); 2,43 (1H, tt, $C_{(11)}H$; 15,0, 7,2, 2,4); 2,53 (1H, d, $C_{(17)}H_B$; 16,8); 2,63 (1H,d, $C_{(17)}H_A$; 16,8); 2,83 (1H,tt, $C_{(6)}H_e$; 16,2, 3,0, 3,0); 3,00 (1H, dtd, $C_{(6)}H_a$; 16,2, 13,2, 3,0); 3,28 (1H, ddd, $C_{(7)}H_a$; 13,2, 13,2, 3,0); 3,85 (3H,s, OCH₃); 3,88 (3H,s, OCH₃); 4,27 (1H, tt, $C_{(7)}H_e$); 13,2, 3,0, 3,0); 4,91 (1H,d. $C_{(9)}H$; 2,4); 6,62 (1H,arom.m.); 6,66 (1H,s, arom.m.)

TABLE 1. (continued)

1	2	3	4
IIId* (~5%)			1,08 (t, $C_{(11)}CH_2\underline{CH_3}$; 7,2); 4,64 (d, $C_{(9)}H$; 3,6)
IIIe	1667, 1595, 1512...1498, 1490 sh, 1452, 1405, 1360, 1337, 1132, 770	201(4,21), 267(4,22), 310(4,20)	0,84 (3H, t, $C_{(9)}CH_2\underline{CH_3}$; 7,5); 1,92...2,12 (2H, m, $C_{(16)}H_2$; 2,05 (1H, m, $C_{(9)}\underline{CH_2}CH_3$; 15,0; 7,5); 2,27 (1H, m, $C_{(9)}\underline{CH_2}CH_3$; 15,0; 7,5); 2,35 (1H, m, $C_{(15)}H$); 2,45 (1H, m, $C_{(15)}H$); 2,71 (1H, d, $C_{(11)}H_B$; 15,6); 2,72 (1H, m, $C_{(17)}H$); 2,81 (1H, d, $C_{(11)}H_A$; 15,6); 2,87 (1H, m $C_{(17)}H$); 2,96...3,13 (2H, m, $C_{(6)}H_a$, $C_{(6)}H_e$); 3,60 (1H, dtd $C_{(7)}H_a$; 13,2, 12,0; 4,2); 4,21 (1H, tt, $C_{(7)}H_e$; 13,2, 4,2, 4,2); 7,17...7,33 (4H, arom.m)
III f	1682, 1613, 1510, 1458, 1360, 1340, 1260	204(4,45), 231(3,82), 267(4,08), 296(3,97), 300(4,04)	0,87 (3H, t, $C_{(9)}CH_2\underline{CH_3}$; 7,2); 1,92...2,13 (2H, m, $C_{(16)}H_2$); 1,97 (1H, m, $C_{(9)}\underline{CH_2}CH_3$; 15,6; 7,2); 2,27 (1H, m, $C_{(9)}\underline{CH_2}CH_3$; 15,6, 7,2); 2,36 (1H, m, $C_{(15)}H_2$); 2,47 (1H, m, $C_{(15)}H_2$); 2,73 (1H, d, $C_{(11)}H_B$; 15,6); 2,74 (1H, m, $C_{(17)}H_2$); 2,80 (1H, d, $C_{(11)}H_A$; 15,6); 2,89 (1H, m $C_{(17)}H_2$); 2,92, (1H, tt, $C_{(6)}H_e$; 15,6, 4,2, 4,2); 3,02 (1H, dtd, $C_{(6)}H_a$; 15,6, 12,0, 4,2); 3,60 (1H, dtd. $C_{(7)}H_a$; 13,2, 12,0, 4,2); 3,85 (3H, s. OCH_3); 3,89 (3H, s, OCH_3); 4,23 (1H, tt, $C_{(7)}H_e$; 13,2, 4,2, 4,2); 6,62 (1H, arom.s); 6,65 (1H, arom.m)
III g	1680, 1612, 1515, 1505, 1490, 1475, 1468, 1452, 1440, 1340	199(4,26), 266(4,14), 311(4,17)	0,83 (3H, t, $C_{(9)}CH_2\underline{CH_3}$; 7,2); 1,11 (3H, s, $C_{(16)}CH_3$); 1,13 (3H, s, $C_{(16)}CH_3$); 2,02 (1H, m. $C_{(9)}\underline{CH_2}CH_3$); 2,29 (2H, s, $C_{(15)}H_2$); 2,32 (1H, m, $C_{(9)}\underline{CH_2}CH_3$); 2,59 (1H, d, $C_{(17)}H_B$; 16, 2); 2,61 (1H, d $C_{(17)}H_A$; 16,2); 2,70 (1H, d, $C_{(11)}H_B$; 15,6); 2,78 (1H, d, $C_{(11)}H_A$; 15,6); 3,03 (2H, m. $C_{(6)}H_a$, $C_{(6)}H_e$; 3,57 (1H, dtd. $C_{(7)}H_a$; 13,2, 12,0, 4,8); 4,23 (1H, tt, $C_{(7)}H_e$; 13,2, 4,8, 4,8); 7,13...7,36 (4H, arom. m
IIIh	1682, 1610, 1525...1480, 1455, 1425, 1380, 1360, 1330, 1186, 1140	199 (4,29), 265 (4,25), 309(4,19)	0,71 (3H, t, $C_{(11)}CH_2\underline{CH_3}$; 7,0); 0,78 (1H, m., $C_{(11)}\underline{CH_2}CH_3$); 0,80 (3H, t, $C_{(9)}CH_2\underline{CH_3}$; 7,0); 1,16 (1H, m, $C_{(11)}\underline{CH_2}CH_3$); 1,97 (2H, m, $C_{(16)}H_2$); 2,06 (1H, m $C_{(15)}H$); 2,23 (1H, dd $C_{(11)}H$); 2,42 (2H, m, $C_{(9)}\underline{CH_2}CH_3$; 7,0); 2,43 (1H, m., $C_{(15)}H$); 2,72 (1H, tt $C_{(17)}H$; 16,0; 6,0; 6,0); 2,86 (1H, tt., $C_{(17)}H$; 16,0, 6,0, 6,0); 2,96 (2H, m, $C_{(6)}H_a$, $C_{(6)}H_e$); 3,49 (1H, m, $C_{(7)}H_a$; 13,0, 9,0, 4,0); 4,30 (1H, m., $C_{(7)}H_e$; 13,0, 4,0, 4,0); 7,10...7,39 (4H, arom.m)

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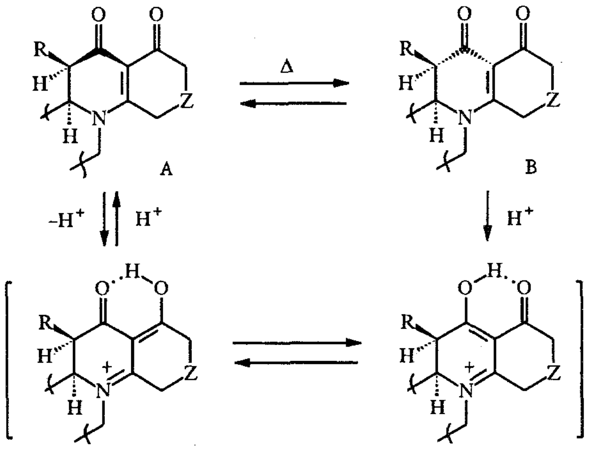
*Proton resonance signals of conformer B, different from signals of conformer A.

Scheme 2



IV

C-ring azasteroid conformers IIIa-d indicate the noncoplanar nature of the α-acyl-β-aminovinylcarbonyl segment. As a result they also indicate the absence of a cross-conjugated state, and of the conjectured coplanarity of all the segments involved in the reaction. In combination with the data on the spontaneous stereoisomerization at $C_{(17)}$ of the methoxycarbonyl derivatives of the 8-azasteroids [1, 5], this result confirms our conclusion concerning the dynamic processes occurring in this particular segment; the phenomenon of mesomeric tautomerism lies at the basis of these processes [11, 12].

EXPERIMENTAL

The reactions were monitored and the individuality of the 8-aza-D-homogonanes IIIa-h was determined by thin-layer chromatography on Silufol UV-254 plates. The eluent was 9.5:0.5 chloroform:methanol; development was in UV light or with iodine vapor. Melting points were determined with a Boetius heating block. IR spectra were obtained with a UR-20 apparatus in KBr tablets. Electron spectra were obtained with Specord UV-vis and M-400 spectrometers. PMR spectra were obtained with a Bruker AC-200 apparatus (200 MHz) with $CDCl_3$ in TMS as internal standard. Mass spectra were obtained with a variant MAT-31 spectrometer with direct introduction of sample; electron ionization energy was 70 eV.

C, H, and N contents agreed with the calculated values.

Results of the spectral studies of compounds IIIa-h are given in Table 1.

11-Ethyl-8-aza-D-homogona-1,3,5(10),13-tetraen-12,17a-dione (IIIa, $C_{19}H_{21}NO_2$). A mixture of 2.62 g (20 mmoles) of 3,4-dihydroisoquinoline (Ia) and 3.64 g (20 mmoles) of 2-butanoyldihydroresorcinol (IIc) in 40 ml of ethanol was boiled for 3 h. The solvent was removed by evaporation and the residue was dissolved in chloroform and filtered through 5 g of silica gel. The filtrate was evaporated and the residue was crystallized from 1:5 ethanol—ether. Yield of IIIa, 5.3 g (89.7%), mp 183-186°C.

2,3-Dimethoxy-11-ethyl-8-aza-D-homogona-1,3,5(10),13-tetraen-12,17a-dione (IIIb, $C_{21}H_{25}NO_4$). A mixture of 3.82 g (20 mmoles) of 3,4-dihydroisoquinoline (Ic) and 3.64 g (20 mmoles) of β-triketone IIc in 30 ml of ethanol was boiled for 4 h; then it was worked up as described above. Yield of IIIb, 6.21 g (87.4%), mp 247°C (1:3 ethanol—ether).

15,16-Dimethyl-11-ethyl-8-aza-D-homogena-1,3,5(10),13-tetraene-12,17a-dione (IIIc, $C_{21}H_{25}NO_4$). A mixture of 2.62 g (20 mmoles) of 3,4-dihydroisoquinoline (Ia) and 4.2 g (20 mmoles) of 2-butanoyldimedon (IId) in 20 ml ethanol was boiled for 3 h. After the usual workup (see above), the yield of IIIc was 5.03 g (77.8%), mp 143-146°C (1:3 ethanol—ether).

2,3-Dimethoxy-16,16-dimethyl-11-ethyl-8-aza-D-homogeno-1,3,5(10),13-tetraen-12,17a-dione(IIId, $C_{23}H_{29}NO_4$). A mixture of 3.82 g (20 mmoles) of dihydroisoquinoline (Ic) and 4.2 g (20 mmoles) of β-triketone IId in 30 ml of ethanol was boiled for 5 h. After workup the yield of IIId was 6.2 g (80.8%), mp 241-243°C (2:3 ethanol—ether).

9-Ethyl-8-aza-D-homogeno-1,3,5(10),13-tetraen-12,17a-dione (IIIe, $C_{19}H_{21}NO_2$). A mixture of 2.4 g (15 mmoles) of 3,4-dihydroisoquinoline (Ib) and 2.3 g (15 mmoles) of 2-acetyldihydroresorcinol (IIa) in 30 ml of ethanol was boiled for 21 h. After workup the yield of IIIe was 1.54 g (34.8%), mp 142-144°C (1:2 ethanol—water).

2,3-Dimethoxy-9-ethyl-aza-D-homogeno-1,3,5(10),13-tetraen-12,17a-dione (IIIf, $C_{21}H_{25}NO_4$). A mixture of 2.19 g (10 mmoles) of 3,4-diisoquinoline (Id) and 1.54 g (10 mmoles) of β-triketone IIa in 35 ml of ethanol was boiled for 40 h. After workup the yield of IIIf was 1.3 g (36.6%), mp 234-235°C (2:3 ethanol—ether).

16,16-Dimethyl-9-ethyl-8-aza-D-homogeno-1,3,5(10),13-tetraen-12,17a-dione (IIIg, $C_{21}H_{25}NO_2$). A mixture of 2.4 g (15 mmoles) of 3,4-dihydroisoquinoline and 2.7 g (15 mmoles) of 2-acetyldimedon (IIb) in 20 ml of ethanol was boiled for 28 h. After workup the yield of IIIg was 2.5 g (51.5%), mp 178-182°C (1:2 ethanol—ether).

9,10-Diethyl-8-aza-D-homogono-1,3,5(10),13-tetraen-12,17a-dione (IIIh, $C_{21}H_{25}NO_2$). A mixture of 1.59 g (10 mmoles) of 3,4-dihydroisoquinoline (Ib) and 1.82 g (10 mmoles) of β-triketone IIc in 20 ml of ethanol was boiled for 50 h. The solvent was removed by evaporation. The residue was dissolved in 40 ml of chloroform and washed with 10% sodium bicarbonate solution and water. Then it was dried over sodium sulfate and filtered through 10 g of silica gel (with washing with chloroform). The filtrate was evaporated and the residue was crystallized to give 0.5 g (15.5%) of IIIh, mp 208-210°C (1:10 ethanol—ether).

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