STRUCTURE AND PROPERTIES OF 8-AZASTEROIDS SYNTHESIZED BY REGIO- AND STEREOSELECTIVE ANNELATION OF 3,4-DIHYDROISOQUINOLINES BY ASYMMETRIC 2-ACYL-1,3-CYCLOHEXANEDIONES

A. L. Mikhal'chuk, O. V. Gulyakevich, D. B. Rubinov, and A. A. Akhrem

It was found that annelation of 3,4-dihydroisoquinolines by 2-acyl-1,3-cyclohexanediones takes place regio- and stereoselectively, leading to $C_{(11)}$- and $C_{(17)}$-substituted derivatives of the 8-aza-D-homogonane series with a trans-disposition of the substituents (Me, Br, Cl, COOMe) at the above positions relative to the angular substituent (H, Me) at $C_{(9)}$. It was shown that the $C_{(17)}$-halogen and methoxycarbonyl derivatives exist in crystals in the form of one stereoisomer, while in solutions as a mixture of stereoisomers, caused by a keto-enol tautomerism of the $C_{(17a)}$-carbonyl. In solutions of acids, these derivatives exist in $N_{(8)} - \ldots - C_{(17a)}$ immonium-enol form, as one stereoisomer. It was found that the $C_{(11)}$-methyl derivatives are obtained in the form of two restrained conformers with respect to ring C, which on boiling are reduced to one conformer. The assignment of the enol regiomers of 4-substituted 2-acetyldimedones has been carried out.

It was known that cyclic Schiff bases and azomethines are annelated by β-di- and tricarbonyl compounds, thus ensuring a simple and effective approach to 8-azasteroids by a one-stage AB + D → ABCD scheme [1-4]. Considering that the above reaction is a key stage in the formation of polycyclic skeletons of compounds used in the production of drugs with a given biological activity [5-7], it was of interest to determine their regio- and stereo-selectivity. The data obtained up to the present time, based on the inclusion in this reaction of symmetrical β-triketones, and also β-tricarbonyl compounds, in particular dihydrodehydroacetic, acetyltetronic and acetyltetramic acids [8-10], which are essentially 2-carboxy-substituted β-diketones, do not give information on their regio- and stereoselectivity. To study the above problems, to determine the limits of applicability of this reaction, and to broaden the series of 8-azagonane and 8-aza-D-homogonane derivatives, we have carried out the synthesis of asymmetric 2-acyl-1,3-cycloalkanediones (Id-f) and studied their reaction with 3,4-di-hydroisoquinolines (IIa-d).

As the starting Schiff bases and azomethines we used the 3,4-dihydroisoquinolines IIa-d, which are readily accessible by the Bischler–Napieralski reaction [11], and as the β-tricarbonyl compounds – 2-propionyl-1,3-cycloalkanediones Ia-c and 4-substituted 2-acetyldimedones Id-f. 2-Propionylcyclopentadione Ia, -dihydroresorcinol Ib, and -dimedone Ic were obtained under the conditions of the previously described O,C-rearrangement of the enol ethers of the corresponding β-diketones by the action of aluminum chloride in dichloroethane [12]. 2-Acetyl-4-methoxycarbonyldimedone Id was obtained by the isomerization of the regioisomeric mixture of enol acetates of carbomethoxydimedone by the action of zinc chloride or 4-dimethylaminopyridine [13], since the use of aluminum chloride as a catalyst did not give the desired β-triketone. 2-Acetyl-4-chlorodimedone If was obtained according to a method described in [14], while the 4-bromo derivative Ie – by the bromination of 2-acetyldimedone. The structure of triacetylmethanes Ia, d, e obtained was confirmed by the whole set of physicochemical data (Tables 1, 2) and also by their comparison with the data for the related β-triketones [12, 14].

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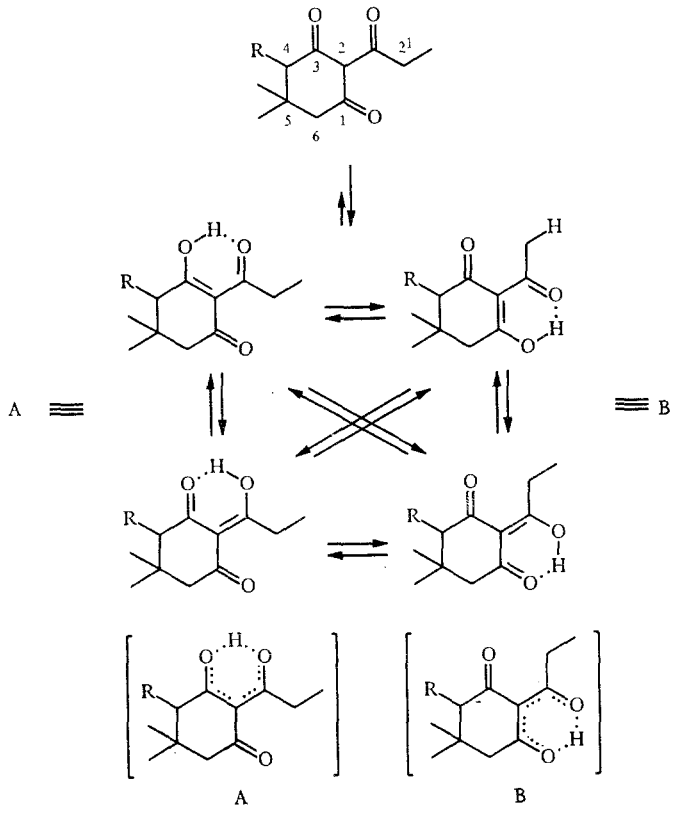
TABLE 1. Yields, Constants, and Spectral Analysis Data of 2-Acyl-1,3-cyclo-alkanediones Ia, d, e

Compound	mp, °C (ether–hexane)	$[M]^+$	M	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Yield, %
Ia	94...96	154	154,17	1705, 1635, 1587, 1440, 1410, 1305, 1247, 1145, 913	239 (3,97), 276 (3,93)	39
Id	80...82	240	240,26	1747, 1660, 1560, 1460, 1238	237 (3,96), 274 (3,99)	82
Ie	60...61	260...261	261,11	1665, 1570, 1450	247 (3,90), 277 (4,00)	81

Scheme 1



Examination of β-triketones Id, e, f by the PMR method showed that the latter exist in the form of two regioisomeric enols A and B (Scheme 1) with a ratio from 1/9 to 3/7 due to a shift of the keto-enol tautomeric equilibrium in the direction of the enol forms and tunneling of the proton between the exo- and endo-cyclic enols resulting in the absence of differences between these enols on the NMR time scale. This explanation agrees well with the results of the investigations of the heteronuclear Overhauser effect, carried out on the example of acetyldimedone [15], and the vibrational spectroscopy data showing the absence of absorption bands of the enolic OH both in solutions and in the crystalline state, and also by the data of microwave spectroscopy [16], a solid phase NMR [17], and of X-ray diffraction analysis [8] for β-dicarbonyl compounds. Data on the assignment of enol regiomers in the series of 2-acyl-1,3-cycloalkanediones are not available in the literature. We found (Table 2) that during the realization of enol regiomers (A) the $C_{(6)}$ AB methylene group present in the α-position with respect to the nonenolized carbonyl group at $C_{(1)}$, has a high absolute value of the SSCC (J = 18-19.5 Hz), while in the case of regiomers (B), the $C_{(6)}$ AB methylene group located in the α-position to the "partially" enolized carbonyl group at $C_{(1)}$ has a lower SSCC (J = 15.5-17 Hz), which is due to the difference of the π-electronic contributions of AB-methylene groups to the observed SSCC.

In the case of 2-propionyl-1,3-cyclopentanedione Ia, the exocyclic enol is probably preferentially or exclusively realized, which can be concluded from the PMR data (Table 2), where the signals of the methylene groups at $C_{(4)}$ and $C_{(5)}$ at 2.52 and 2.78 ppm represent a system which can be referred to the A_2B_2 type [19]. This assignment agrees well with the results of the investigation carried out on the example of 2-acetyl-1,3-cyclopentanedione [20].

TABLE 2. PMR Spectra of 2-Acyl-1,3-cycloalkanediones Ia, d-f

Compound	Regiomer	δ, ppm (SSCC, J, Hz)
Ia		1,14 (3H, t, $C_{(2')}CH_3$, 7,5); 2,52 and 2,78 (2H and 2H, m and m, $C_{(4)}H_2$ and $C_{(5)}H_2$); 2,96 (2H, q $C_{(2')}H$, 7,5); 17,95 (1H, s, OH)
Id	A (85%)	1,13 and 1,15 (3H and 3H, s and s, $C_{(5)}(CH_3)_2$); 2,47 (1H, d, $C_{(6)}H_B$, 18,0); 2,64 (3H, s, $C_{(2)}COCH_3$); 2,79 (1H, d, C_6H_A, 18,0); 3,34 (1H, s, $C_{(4)}H$); 3,37 (3H, s, $C_{(4)}COOCH_3$); 18,23 (1H, s, OH)
	B (15%)	1,11 and 1,13 (3H and 3H, s and s, $C_{(5)}CH_3$); 2,28 (1H, d, $C_{(6)}H_B$, 15,0); 2,69 (3H, s, $C_{(2)}COCH_3$); 2,79 (1H, d, $C_{(6)}H_A$, 15,0); 3,45 (1H, s, $C_{(4)}H$); 3,81 (3H, s, $C_{(4)}COOCH_3$); 18,02 (1H, s, OH)
Ie	A (90%)	1,22 (6H, s, $C_{(5)}(CH_3)_2$); 2,41 (1H, dd, $C_{(6)}H_B$, 19,9, 2,0); 2,62 (3H, s $C_{(2)}COCH_3$); 2,94 (1H, d, $C_{(6)}H_A$, 19,0); 4,16 (1H, d, $C_{(4)}H$, 2,0); 18,18 (1H, s, OH)
	B (10%)	1,19 (6H, s, $C_{(5)}(CH_3)_2$); 2,30 (1H, dd, $C_{(6)}H_B$, 16,5, 2,0); 2,65 (3H, s $C_{(2)}COCH_3$); 2,76 (1H, d, $C_{(6)}H_A$, 16,5); 4,40 (1H, d, $C_{(4)}H$; 2,0); 17,94 (1H, s, OH)
If	A (95%)	1,20 and 1,22 (3H and 3H, s and s, $C_{(5)}(CH_3)_2$); 2,46 (1H, d, $C_{(6)}H_B$, 18,5); 2,62 (3H, s, $C_{(2)}COCH_3$); 2,90 (1H, d, $C_{(6)}H_A$, 18,5); 4,08 (1H, s, $C_{(4)}H$); 18,16 (1H, s, OH)
	B (5%)	1,20 and 1,22 (3H and 3H, s and s, $C_{(5)}(CH_3)_2$); 2,30 (1H, d, $C_{(6)}H_B$, 16,5); 2,64 (3H, s, $C_{(2)}COCH_3$); 2,76 (1H, d, $C_{(6)}H_A$, 16,5); 4,32 (1H, s, $C_{(4)}H$); 17,94 (1H, s, OH)

TABLE 3. Yields, Physical Constants, and Spectral Analysis Data of 8-Azasteroids IIIa-i

Compound	mp, °C	$[M]^+$	M	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Yield, %
IIIa	242	327	327,37	1705, 1620, 1600 sh 1575, 1525	232 (3,85), 258 (4,35), 288 (4,21)	36,7
IIIb	247 (dec.)	355	355,42	1678, 1612, 1515, 1505	203 (4,73), 234 (4,03), 266 (4,32), 296 sh (4,26), 305 (4,28)	35,7
IIIc	184...187	369	369,44	1680, 1610, 1526	203 (4,60), 233 (3,95), 268 (4,15), 307 (4,22)	81,3
IIId	202	353	353,40	1740, 1680, 1610, 1515, 1225	203 (4,22), 268 (4,11), 308 (4,27)	51,8
IIIe	220...223	367	367,43	1742, 1675, 1605, 1522, 1450, 1239	199 (4,33), 208 (4,12), 272 (4,18), 307 (4,29)	27,2
IIIf	202...204	413	413,45	1750, 1685, 1615, 1525, 1231	204 (4,62), 229 (4,00), 272 (4,18), 307 (4,28)	60,0
IIIg	212 (dec.)	433...435	434,33	1688, 1615, 1516	207 (4,04), 296 sh (4,30), 310 (4,35)	82,9
IIIh	215 (dec.)	329...330	329,83	1689, 1621, 1530	199 (4,30), 271sh (4,05), 308 (4,29)	67,5
IIIi	226 (dec.)	389...390	389,88	1688, 1615, 1515	205 (4,54), 230 (3,88), 280 sh (4,07), 307 (4,23)	85,9

*The melting points were determined for the samples after additional crystallization of the ethanol–ether mixture (1:3).

**IIIg Hal; = Br, IIIh, i Hal = Cl.

Annelation of 3,4-dihydrosoquinolines IIa-d by β-triketones Ia-f effected by boiling their equimolar mixtures in ethanol for 3-40 h, leads to 8-azagonane (IIIa) and 8-aza-D-homogonanes IIIb-i. Thus, in the reaction of β-triketones Ia-c with 3,4-dihydroisoquinolines IIb-d, $C_{(11)}$-methyl-substituted derivatives IIIa-c were obtained with a trans-disposition of the $C_{(11)}$-methyl groups relative to the proton or methyl at $C_{(9)}$ of IIIa, c and IIIb, respectively. This conclusion follows from the analysis of the vicinal SSCC of protons at $C_{(9)}$ and $C_{(11)}$. It is noteworthy that the derivative IIIa was obtained in the form of a chromatographically inseparable mixture of two restrained conformers in a ratio of 3:7, as indicated by the presence in the PMR spectrum of additional signals, in particular, for $C_{(9)}H_a$ and $C_{(11)}Me$. Thus, together with the $C_{(9)}H_a$ signal δ 4.99 d ppm ($J_{(9)}H_a:C_{(11)}H_e$ = 4.0 Hz) there is in the spectrum a signal at δ 4.55 d ppm (J ($C_{(9)}H_a:C_{(11)}H_e$ = 7.2 Hz) and together

TABLE 4. PMR Spectra of 8-Azasteroids IIIa-i

Compound	δ, ppm (SSCC), J, Hz
1	2
IIIa	1,30 (3H, d, $C_{(11)}CH_3$, 7,2); 2,51 (2H, m, $C_{(15)}H_2$); 2,7 (1H, s, $C_{(11)}H$, 7,2); 2,74...3,20 (4H, m, $C_{(6)}H_a$, $C_{(6)}H_e$, $C_{(16)}H_2$); 3,63 (1H, q.q, $C_{(7)}H_a$, 13,0, 10,0, 5,0); 3,84 (3H, s OCH_3); 3,86 (3H, s, OCH_3); 4,06 (1H, q.q, $C_{(7)}H_e$, 13,0, 6,0, 3,5); 4,55 (1H, d, $C_{(9)}H_a$, 7,2), 6,68& 6,70, (1H & 1H, s&s, $C_{(1)}H$ & $C_{(4)}H$)
IIIb	0,66 (3H, d, $C_{(11)}CH_3$, 7,2); 1,61 (3H, s, $C_{(9)}CH_3$); 2,02 (1H, s, $C_{(16)}H$); 2,12 (1H, m $C_{(16)}H$); 2,34 (1H, d.t.d, $C_{(17)}H_a$, 16,2, 12,0, 4,8); 2,48 (1H, t.t, $C_{(15)}H_e$, 18,0, 4,8 4,8); 2,53 (1H, q, $C_{(11)}H_e$, 7,2); 2,66 (1H, q.q, $C_{(17)}H_e$, 16,2, 10,5, 5,4); 2,79...2,88 (2H, m, $C_{(6)}H_e$, $C_{(15)}H_a$); 2,99 (1H, d.d.d.d, $C_{(6)}H_a$, 16,2, 13,2, 2,4); 3,35 (1H, d.d. d, $C_{(7)}H_a$, 13,2, 13,2, 3,6); 3,85 (3H, s, OCH_3); 3,91 (3H, s, OCH_3), 4,26 (1H, q.q $C_{(7)}H_e$, 13,2, 4,2, 2,4); 6,54 & 6,62 (1H and 1H, $C_{(1)}H$ & $C_{(4)}H$)
IIIc	1,08 & 1,11 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 1,23 (2H, d, $C_{(11)}CH_3$, 7,2); 2,25 (2H, s, $C_{(17)}H_2$); 2,47 (1H, d, $C_{(15)}H_B$, 15,6); 2,60 (1H, d, $C_{(15)}H_A$, 15,6); 2,71 (1H, s, $C_{(11)}H$, 7,2); 2,92 (1H, t.t, $C_{(6)}H_e$, 16,5, 3,6, 3, 6); 3,09 (1H, d.t.d, $C_{(6)}H_a$, 15,6, 11,0, 5,4); 3,55 (1H, q.d.k, $C_{(7)}H_a$, 12,6, 11,0, 3,6); 3,85& 3,88 (3H & 3H, s & s, $2OCH_3$); 4,19 (1H, q.q, $C_{(7)}H_e$, 12,6, 5,4, 3, 6); 4,47 (1H, d, $C_{(9)}H_a$, 7,2); 6,68 & 6,69 (1H& 1H, s & s, $C_{(1)}H$ & $C_{(4)}H$)
IIId	1,16 (6H, s, $C_{(16)}(CH_3)_2$); 2,51 (1H, d, $C_{(15)}H_M$, 17,4); 2,62 (1H, t, $C_{(11)}H_B$, 15,6, 15,6); 2,84 (1H, d.d, $C_{(11)}H_A$, 15,6, 4,8); 2,98 (1H, t.t, $C_{(6)}H_e$, 15,6, 3,6, 3,6); 3,09 (1H, d.t.d, $C_{(6)}H_a$, 15,6, 9,8, 3,6); 3,14 (1H, d, $C_{(15)}H_A$, 17,4); 3,20 (1H, s, $C_{(17)}H$); 3,45 (1H, d.t.d, $C_{(7)}H_a$; 13,2, 9.8, 3,6); 3,67 (3H, s, $C_{(17)}COOCH_3$); 4,24 (1H, t.t. $C_{(7)}H_e$, 13,2, 3,6, 3,6); 4,95 (1H, d.d, $C_{(9)}H_a$, 15,6, 4,8); 7,11...7,33 (4H, m, $C_{(1)}$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)
IIId*	1,15 & 1,18 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 2,47 (1H, d, $C_{(15)}H_M$, 17,5); 2,66 (1H, d.d. $C_{(11)}H_B$, 16,2, 4,2); 2,79 (1H, d.d., $C_{(11)}H_A$, 16,2, 15,0); 2,97 (1H, t.t, $C_{(6)}H_e$, 16,0, 3,6, 3,6); 3,13 (1H, d, $C_{(15)}H_A$, 17,5); 3,15 (1H, d.d.d., $C_{(6)}H_a$, 16,0, 12,5, 3,6); 3,25 (1H, s, $C_{(17)}H$); 3,45 (1H, d.d.d., $C_{(7)}H_a$, 12,5, 12,5, 3,6); 3,69 (3H, s, $C_{(17)}COOCH_3$); 4,21 (1H, t.t, $C_{(7)}H_e$, 12,5, 3,6, 3,6); 4,90 (1H, d.d., $C_{(9)}H_a$, 15,0, 4,2); 7,13...7,35 (4H, m, $C_{(1)}H$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)
IIIe	1,14 & 1,16 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 1,62 (3H, s, $C_{(9)}CH_3$); 2,42 (1H, d, $C_{(15)}H_B$, 18,0); 2,66 (1H, d, $C_{(11)}H_B$, 16,0); 2,80 (1H, d., $C_{(15)}H_A$, 18,0); 2,82 (1H, d., $C_{(11)}H_A$, 16,0); 2,95 (1H, t.t $C_{(6)}H_e$, 12,0, 3,6, 3,6); 3,14 (1H, d.t.d, C(6)Ha, 13,5, 12,0, 3,6); 3,20 (1H, s., $C_{(17)}H$); 3,40 (1H, d.d.d...., $C_{(7)}H_a$, 13,5, 13,5, 3,6); 3,66 (3H, s, $C_{(17)}COOCH_3$); 4,28 (1H, t.t, $C_{(7)}H_e$, 13,5, 3,6, 3,6); 7,10...7,34 (4H, m., $C_{(1)}H$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)
IIIf	1,15& 1,16 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 2,49 (1H, d, $C_{(15)}H_M$, 18,0); 2,59 (1H, t $C_{(11)}H_a$, 15,6); 2,83 (1H, d.d, $C_{(11)}H_e$, 15,6, 3,6); 2,88 (1H, t.t, $C_{(6)}H_e$, 15,6, 3,0, 3,0); 3,05 (1H, d.t.d, $C_{(6)}H_a$, 15,6, 10,8, 3,0); 3,15 (1H, d, $C_{(15)}H_A$, 18,0); 3,20 (1H, s $C_{(17)}H$); 3,39 (1H, d.t.d., $C_{(7)}H_a$, 13,2, 10,8, 3,0); 3,68 (3H, s., $C_{(17)}COOCH_3$); 3,85 (3H, s, OCH_3); 3,89 (3H, s, OCH_3); 4,24 (1H, t.t, $C_{(7)}H_e$, 13,2, 3,0, 3,0); 4,88 (1H, d.d, $C_{(9)}H_a$, 15,6, 3,6); 6,61 & 6,69 (1H & 1H, s & s, $C_{(1)}H$ and $C_{(4)}H$)
IIIf**	1,14 & 1,20 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 2,45 (1H, d, $C_{(15)}H_M$, 18,0); 2,63 (1H, t, $C_{(11)}H_a$, 15,6); 2,78 (1H, d.d., $C_{(11)}H_e$, 15,6, 3,6); 3,13 (1H, d, $C_{(15)}H_A$, 18,0); 3,24 (1H, s, $C_{(17)}H$); 3,69 (3H, s, $C_{(17)}COOCH_3$); 3,84 & 3,87 (3H & 3H, s & s, $2OCH_3$); 4,22 (1H, t.t., $C_{(7)}H_e$, 13,2, 3,6, 3,6); 4,82 (1H, d.d., $C_{(9)}H_a$, 15,6, 3,6)
IIIg	1,22 & 1,26 (3H and 3H, s & s, $C_{(16)}(CH_3)_2$); 2,46 (1H, d, $C_{(15)}H_M$, 16,5); 2,62 (1H, d.d $C_{(11)}H_a$, 16,0, 14,0); 2,78 (1H, q, $C_{(11)}H_e$, 16,0, 4,5); 2,86 (1H, t.t, $C_{(6)}H_e$, 15,0, 5,0, 5,0); 2,96 (1H, d, $C_{(15)}H_A$; 16,5); 3,08 (1H, d.d.d, $C_{(6)}H_a$, 15,0, 12,0, 5,0); 3,40 (1H, d.d.d, $C_{(7)}H_a$, 15,0, 12,0, 5,0); 3,82 (3H, s, OCH_3); 3,86 (3H, s, OCH_3); 4,08 (1H, s $C_{(17)}H$); 4,18 (1H, t.t, $C_{(7)}H_e$, 15,0, 5,0, 5,0); 4,84 (1H, d.d, $C_{(9)}H_a$, 14,0, 4,5); 6,58 & 6,66 (1H and 1H, $C_{(1)}H$ and $C_{(4)}H$)
IIIh	1,18 (6H, s, $C_{(16)}(CH_3)_2$); 2,47 (1H, d, $C_{(15)}H_M$, 17,0), 2,65 (1H, q, $C_{(11)}H_B$, 17,0, 14,0); 2,82 (1H, d.d, $C_{(11)}H_A$, 17,0, 5,0); 2,96 (1H, d, $C_{(15)}H_A$, 17,0); 2,97 (1H, t.t $C_{(6)}H_e$, 11,0, 4,0, 4,0); 3,13 (1H, d.d.d, 14,0, 11,0; 4,0); 3,43 (1H, d.d.d, $C_{(7)}H_a$, 14,0, 12,0, 4,0); 4,02 (1H, s, $C_{(17)}H$); 4,17 (1H, t.t, $C_{(7)}H_e$, 12,0, 4,0, 4,0); 4,90 (1H, d.d. $C_{(9)}H_a$, 14,0, 5,0); 7,10...7,36 (4H, m, $C_{(1)}H$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$)
IIIi	1,18 & 1,20 (3H & 3H, s & s, $C_{(16)}(CH_3)_2$); 2,48 (1H, d, $C_{(15)}H_M$, 17,0); 2,62 (1H, q $C_{(11)}H_a$, 16,0, 15,0); 2,78 (1H, d.d, $C_{(11)}H_e$, 16,0, 4,0); 2,86 (1H, t.t., $C_{(6)}H_e$, 15,0, 4,0, 4,0); 2,95 (1H, d, $C_{(15)}H_A$, 17,0); 3,06 (1H, d.d.d., $C_{(6)}H_a$, 15,0, 12,0, 4,1); 3,38 (1H, d.d.d., $C_{(7)}H_a$, 15,0, 12,0, 4,0); 3,82 (3H, s, OCH_3); 3,86 (3H, s, OCH_3); 4,02 (1H, s, $C_{(17)}H$); 4,20 (1H, t.t, $C_{(7)}H_e$, 15,0, 4,0, 4,0); 4,82 (1H, d.d, $C_{(9)}H_a$, 15,0, 4,0); 6,58 & 6,66 (1H & 1H, s & s, $C_{(1)}H$ & $C_{(1)}H$)

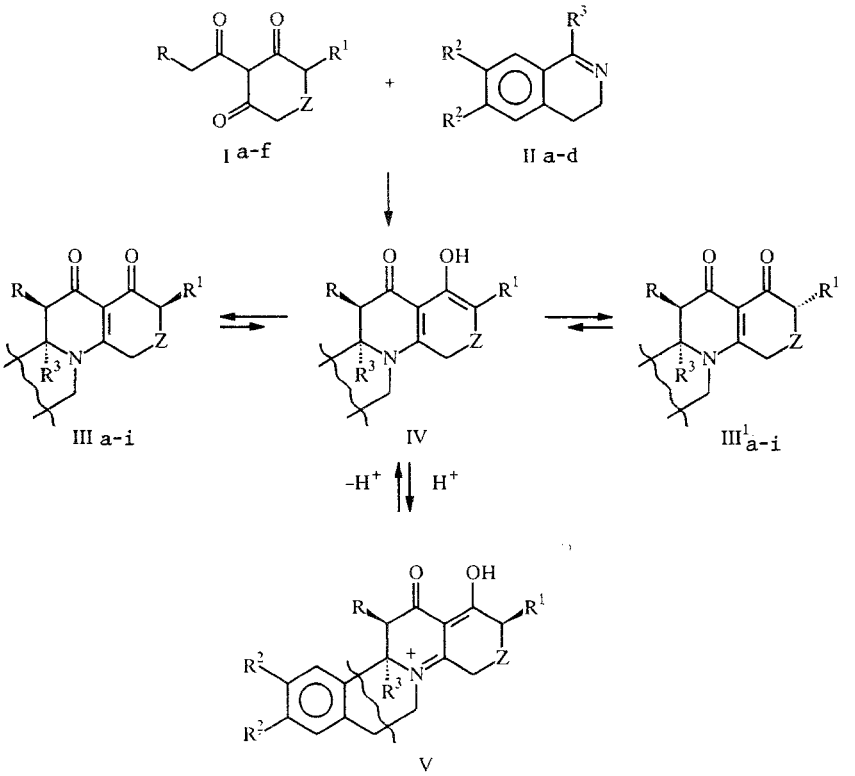
*The spectrum was obtained in the presence of 1 equimole of HCOOH.

**Additional signals in the spectrum of IIIf after a 7-h exposure of the sample. The $C_{(6)}H_e$, $C_{(6)}H_a$, $C_{(7)}H_a$, $C_{(1)}H$, and $C_{(4)}H$ signals remained unchanged and are given in the spectrum of IIIf.

with the $C_{(11)}$Me signal δ 0.70 d ppm (J $C_{(11)}$Me:$C_{(11)}H_e$ = 7.2 Hz), there is a signal at δ 1.30 d ppm (J $C_{(11)}$Me:$C_{(11)}H_e$ = 7.2 Hz). However, after boiling part of the IIIa obtained for 7 h in ethanol, only one conformer was obtained (Table 4, IIIa). It can be concluded from these data that the C ring of 8-azagonanes is not planar, as was previously assumed, but can exist in the form of a flattened chair with a $C_{(12)}$ carbonyl group extending forwards and backwards from the plane of the figure (Scheme 2).

By the reaction of 4-substituted β-triketones Id-f and 3,4-dihydroiosquinolines IIa-c, $C_{(17)}$-substituted derivatives of 8-azasterodids IIId-i have been exclusively obtained, which indicates the regoselectivity of the process. This conclusion can be proved by the data on the observation of the homonuclear Overhauser effect between the protons referred to $C_{(15)}H_{(2)}$ and $C_{(7)}H_e$, and the absence of the effect between protons referred to $C_{(17)}H$ and $C_{(7)}H_e$. A distinct property of these compounds is the fact that in the crystalline state they exist in the form of one stereoisomer with a trans-disposition of the substituents at $C_{(17)}$ relative to the proton or methyl group at $C_{(9)}$, as has been found by the x-ray diffraction analysis for IIId, while in solutions, two stereoisomers can be observed, the ratio of which changes depending on the time of exposure of the solution and the solvent used. This behavior of the IIId-i derivatives is explained by the realization in the solutions of the keto-enol tautomeric equilibrium (scheme 2) and conforms with the data obtained as a result of the observations that in the registration of the PMR spectra of compounds IIId-i for 15-20 min after the preparation of the samples only one set of the resonance proton signals is present in the spectrum (Table 4, IIId-i), while after 3-12 h of exposure of the sample, additional signals appear corresponding to another stereoisomer (Table 4, IIIf**).

Scheme 2



Id-f, IIId-i R = H; Ia-c, IIIa-c R = Me; Ia-c, IIIa-c R^1 = H; Id, IIId-f R^1 = COOMe; Ie, IIIg R^1 = Br; If, IIIh-i R^1 = Cl; IIa, c, IIId, e, h R^2 = H; IIb, d, IIIa-c, f, g, i R^2 = OMe; IIa, b, IIIa, c, d, f-i R^3 = H; IIc, d, IIIb, e R^3 = Me; Ia, IIIa Z = −; Ib, IIIb Z = CH_2; Ic-f, IIIc-i, Z = CMe_2.

The stereoisomerization of the 17-halogen- and methoxycarbonyl derivatives IIId-i was also observed by means of a two-dimensional TLC. The attempts to isolate the stereoisomeric IIId′-i′ were unsuccessful, since during the crystallization one stereoisomer with trans-disposition of the substituent at $C_{(17)}$ relative to substituent at $C_{(9)}$ passes exclusively into the crystalline phase. It is noteworthy that the enol form IV was not recorded in either the PMR or in the IR spectra, which can be explained by the extremely low population of the latter. Examination of the stereoisomerization of the methoxycarbonyl derivative IIId in the presence of acids led to an unexpected result. Instead of the expected enol tautomer IV, we observed an enol-immonium derivative (V; IIId*, Table 4). This assignment was based on the fact that in the PMR spectrum there are

resonance signals of a proton at 18.35 ppm and of the $C_{(17)}$-methine proton at 3.25 ppm. The spectrum thus becomes simplified, since signals of only one stereoisomer are observed. The absence of stereoisomers of compounds IIId-i in the presence of acids (formic, trifluoroacetic) can be explained by steric interactions of the vicinal substituents at $C_{(17)}$ and $C_{(16)}$-gem-dimethyl groupings, intensified by the flattening of the ring during the realization of the enol-immonium derivative V. In this case it is energetically preferable for the substituent at $C_{(17)}$ (halogen, COOMe) to occupy a trans-axial position relative to one of the $C_{(16)}$ methyl groups, since at an equatorial disposition it will be subjected to a considerable diequatorial interaction with another group.

In the UV spectra of derivatives IIIa-i two absorption bands are observed at 258-272 nm ($\log\varepsilon$ = 4.05-4.35) and 288-310 nm ($\log\varepsilon$ = 4.21-4.35), characteristic for the series of 8-aza-steroids containing an α-acyl-β-aminovinylcarbonyl (AAVC) fragment, which correspond to the chromophores of the AAVC fragment. Together with the above absorption bands in the absorption spectra of compounds IIIa-c, f-g there are also absorption bands due to the electronic transitions of the dimethoxy-substituted aromatic ring at 229-234 nm ($\log\varepsilon$ = 3.85-4.03). It should be noted that for compounds IIIg-i a considerable bathochromic shift of the absorption maximum of the high-frequency absorption band by 20-25 nm is characteristic.

In the IR spectra of 8-azasteroids IIIa-i there is a group of absorption bands due to the stretching vibrations of the C−N, C=C, and C=O groups of the AAVC fragment at 1705-1678, 1621-1605, 1530-1505 cm^{-1}. For the $C_{(17)}$-methoxycarbonyl-substituted derivatives IIId-f, absorption bands are also observed, which are due to the C−O and C=O stretching vibrations of the ester groups at 1750-1740 and 1235-1225 cm^{-1}, respectively.

Thus, the results obtained indicate that the annelation of the 3,4-dihydroisoquinolines by asymmetric β-triketones is realized exclusively regio- and stereoselectively, leading to $C_{(11)}$- and $C_{(17)}$-derivatives with a trans-disposition of the substituents relative to the substituent (H, Me) at $C_{(9)}$.

EXPERIMENTAL

The synthesis and purity of the compounds obtained were monitored by means of TLC on Silufol UV-254 plates, using a chloroform−methanol (19:1) mixture as eluent, and development in the UV light or by iodine vapors. The melting points were determined on a Boetius heating block. The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets. The UV spectra were run on a Specord UV-Vis spectrometer in $2.5\cdot10^{-4}$-$5.0\cdot10^{-4}$ mole/liter ethanol solutions. The mass spectra were obtained on a Varian MAT-311 spectrometer, with direct introduction of the sample, and the energy of the ionizing electrons of 70 eV. The PMR spectra were obtained on Bruker WM-360 (360 MHz) and Bruker Al-200 spectrometers (200 MHz) in $CDCl_3$ with TMS as internal standard and digital resolution of 0.5 Hz. The yields, melting points, IR, UV, PMR spectroscopy, and mass spectrometry data of the obtained and studied compounds Ia, d-f, and IIIa-i are given in Tables 1-4.

The elemental analysis data for C, H, Br for compounds Ia, d, e correspond to the calculated values.

2-Propionyl-1,3-cyclopentanedione (Ia, $C_8H_{10}O_3$). A solution of 1.96 g (20 mmoles) of 1,3-cyclopentanedione, 1.98 ml (24 mmoles) of pyridine and 2.04 ml (23.5 mmoles) of propionyl chloride in 200 ml of $CHCl_3$ was stirred fr 1 h at room temperature, and then was successively washed with water, 5% hydrochloric acid, water, a 5% solution of sodium bicarbonate, and water again, and dried over freshly calcined magnesium sulfate. The solution was evaporated, the residue was dissolved in 50 ml of dichloroethane, and the solution obtained was added to a suspension of 12 g (90 mmoles) of aluminum chloride in 250 ml of dichloroethane. The reaction mixture was stirred for 4 h at room temperature, and then poured onto 150 g of ice and acidified with 10 ml of conc. hydrochloric acid. The organic layer was separated, dried over sodium sulfate and evaporated. The aqueous layer was extracted with $CHCl_3$ (6 × 50 ml), the combined extracts were dried over sodium sulfate, evaporated, and the residue was combined with the residue of the dichloroethane solution. The combined organic layers were extracted with hexane (4 × 30 ml), from which after the evaporation to a 1/3 of its volume, 1.2 g of β-triketone Ia was isolated.

2-Acetyl-5,5-dimethyl-4-methoxycarbonyl-1,3-cyclohexanedione (Id). A. A stirred suspension of 7.21 g (30 mmole) of an equimolar mixture of 3-acetoxy-5,5-dimethyl-6-methoxycarbonylcyclohex-2-en-1-one and 3-acetoxy-5,5-dimethyl-4-methoxycarbonylcyclohex-2-en-1-one and 6.0 g (45.0 mmoles) of freshly calcined zinc chloride was heated at 80°C for 2 h, then was treated with 50 ml of $CHCl_3$ and filtered off. The filtrate was evaporated and the residue was extracted with hexane. From the organic extracts 5.95 g of β-triketone Id was isolated.

B. A solution of 24.03 g (0.1 mole) of the regioisomeric mixture of 4-methoxycarbonyldimedone enol acetates and 1.0 g of 4-dimethylaminopyridine in 200 ml of toluene was boiled for 3 h, then was washed with 5% HCl, water, and evaporated. Crystallization of the residue from an ether–hexane mixture gave 19.22 g of β-triketone Id, identical with that obtained by method A.

2-Acetyl-4-bromo-5,5-dimethyl-1,3-cyclohexanedione (Ie). A mixture of 1.82 g (10 mmoles) of 2-acetyldimedone and 1.6 g (10 mmoles) of Br_2 in 10 ml of DMF was heated for 1 h at 100°C and was then held for 12 h at room temperature. The mixture was diluted with water, extracted with ether, the extracts were evaporated, and the residue (2.45 g) was chromatographed on 50 g of silica gel (5/40 μ). The elution with ether gave 2.12 g of bromide Ie.

11-Methyl-2,3-dimethoxy-8-azagona-1,3,5(10),13-tetraene-12,17-dione (IIIa). A mixture of 1.91 g (10 mmoles) of 3,4-dihydroisoquinoline IIb and 1.54 g (10 mmoles) of β-triketone Ia in 20 ml of ethanol was boiled for 3 h, the solvent was evaporated, the residue was dissolved in $CHCl_3$ and the solution was chromatographed on 150 g silica gel (100/250 μ), eluting with a $CHCl_3$–MeOH (19:1) mixture. Yield, 1.2 g of 8-azagonane IIIa.

9,11-Dimethyl-2,3-dimethoxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIb). A mixture of 2.05 g (10 mmoles) of 3,4-dihydroisoquinoline IId and 1.68 g (10 mmoles) of β-triketone Ib in 20 ml of ethanol was boiled for 24 h, and the reaction mixture was evaporated. The residue was dissolved in $CHCl_3$ (8-12 ml) and chromatographed on 20 g of silica gel (40/250 μ), eluting with $CHCl_3$. Evaporation of three middle fractions and crystallization from an ethanol–ether mixture gave 1.27 g of 8-aza-D-homogonane IIIb.

11,16,16-Trimethyl-2,3-dimethoxy-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIc). A mixture of 1.91 g (10 mmoles) of 3,4-dihydroisoquinoline IIb and 1.96 g (10 mmoles) of β-triketone Ic in 50 ml of ethanol was boiled for 4 h, and the reaction mixture was evaporated to one-half of its volume. After adding 50 ml of ether the mixture was allowed to stand for 5 h at rom temperature. The crystals that separated out were filtered off and recrystallized from an ethanol–ether (1:5) mixture. Yield, 3.0 g of the 8-azasteroid IIIc.

16,16-Dimethyl-17-methoxycarbonyl-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIId). A mixture of 0.9 g (3.75 mmoles) of β-triketone Id and 0.5 g (3.8 mmoles) of 3,4-dihydroisoquinoline IIa in 10 ml of ethanol was boiled for 2.5 h, and the reaction mixture was then evaporated to 1/3 of its volume, ether was added to a slight turbidity, and the mixture was allowed to stand for 7 h. The crystals that separated out were filtered off, washed with ether and recrystallized from a chloroform–ether (1:7) mixture. Yield, 0.68 g of the 8-azasteroid IIId.

9,16,16-Trimethyl-17-methoxyarbonyl-8-aza-D-homogona-1,3,5-(10)-,13-tetraene-12,17a-dione (IIIe). A mixture of 1.45 g (10 mmoles) of 3,4-dihydroisoquinoline IIc and 2.4 g (10 mmoles) of β-triketone Id in 30 ml of ethanol was boiled for 40 h. The reaction mixture as evaporated, the residue was dissolved in $CHCl_3$, and chromatographed on 35 g of silica gel (100/250 μ), eluting with $CHCl_3$. Crystallization of the residue of the collected eluates from an ethanol–ether (2:5) mixture gave 1.0 g of the 8-azasteroid IIIe.

16,16-Dimethyl-2,3-dimethoxy-17-methoxycarbonyl-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17a-dione (IIIf). A mixture of 0.9 g (3.75 mmoles) of β-triketone Id and 0.7 g (3.66 mmoles) of 3,4-dihydroisoquinoline IIb in 20 ml of ethanol was boiled for 5 h. The reaction mixture was then cooled, and after adding ether to turbidity, was allowed to stand at +5°C for 12 h. The crystals that separated out were filtered off and recrystallized from an ethanol–ether (2:5) mixture. Yield, 0.9 g of the 8-azasteroid IIIf.

17-Bromo-16,16-dimethyl-2,3-dimethoxy-8-aza-D-homogona-1,3,5-(10),13-tetraene-12,17a-dione (IIIg). A mixture of 1.3 g (5.0 mmoles) of β-triketone Ie and 0.95 g (5.0 mmoles) of 3,4-dihydroisoquinoline IIb in 30 ml of ethanol was boiled for 4 h in argon atmosphere. It was then cooled, and after adding ether to a slight turbidity, was allowed to stand at +5°C for 17 h. The crystals that separated out were filtered off and recrystallized from an ethanol–ether (2:5) mixture. Yield, 1.9 g of the 17-bromoderivative IIIg.

16,16-Dimethyl-17-chloro-8-aza-D-homogona-1,3,5-(10),13-tetraene-12,17a-dione (IIIh). A mixture of 0.44 g (3.3 mmoles) of 3,4-dihydroisoquinoline IIa and 0.72 g (3.3 mmoles) of β-triketone If in 10 ml of ethanol was boiled for 3 h in argon atmosphere. In the course of boiling crystals separated out, which after cooling were filtered, washed with ether and recrystallized from an ethanol–ether–chloroform (1:5:3) mixture. Yield, 0.75 g of the 17-chloro derivative IIIh.

16,16-Dimethyl-2,3-dimethoxy-17-chloro-8-aza-D-homogona-1,3,5-(10),13-tetraene-12,17a-dione (IIIi). A mixture of 0.64 g (3.3 mmoles) of 3,4-dihydroisoquinoline IIb and 0.72 g (3.3 mmoles) of β-triketone If in 10 ml of ethanol was boiled for 5 h in argon atmosphere. It was then cooled, diluted with ether to slight turbidity and allowed to stand at room temperature for 17 h. The crystals that separated out were dissolved in $CHCl_3$ and filtered through 10 g of silica gel (5/40 μ), and the filtrate was diluted with ether. Yield, 1.1 g of the 17-chloro derivative IIIi.

The IR spectra were run by L. I. Solovei, the UV spectra by G. S. Yankovskaya, and the PMR spectra were obtained under the direction of E. V. Borisov.

REFERENCES

1. M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., J. Org. Chem., **31,** 797 (1966).
2. A. A. Akhrem, A. M. Moiseenkov, and V. A. Krivoruchnko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2078 (1972).
3. A. A. Akhrem, A. M. Moiseenkov, and A. I. Poselenov, Dokl. Akad. Nauk SSSR, **203,** 95 (1972).
4. A. A. Akhrem and Yu. A. Titov, Total Synthesis of Steroids [in Russian], Nauka, Moscow (1967).
5. A. A. Akhrem, B. B. Kuz'mitskii, F. A. Lakhvich, V. A. Khripach, and Yu. L. Zhuravkov, Chemistry and Biology of Immunoregulators [in Russian], Zinatne, Riga (1985), p. 265.
6. B. B. Kuz'mitskii, O. V. Stoma, L. M. Slepneva, A. E. Mashkovich, V. P. Nasek, O. V. Gulyakevich, and A. L. Mikhal'chuk, Farmakol. Toksikol., **52,** 71 (1989).
7. A. A. Akhrem and A. L. Mikhal'chuk, Summaries of Lectures at the 7th Conference on the Chemistry of Dicarbonyl Compounds [in Russian], Riga (1991), p. 7.
8. A. A. Akhrem, A. M. Moiseenkov, and V. A. Krivoruchko, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1302 (1973).
9. A. A. Akhrem, F. A. Lakhvich, L. G. Lis, and V. N. Pshenichnyi, Dokl. Akad. Nauk Beloruss. SSR, **22,** 431 (1978).
10. A. A. Akhrem, F. A. Lakhvich, V. N. Pshenichnyi, O. F. Lakhvich, and B. B. Kuz'mitskii, Dokl. Akad. Nauk SSSR, **240,** 595 (1978).
11. W. M. Whaley and T. R. Govindachari, Organic Reactions [Russian translation], Vol. 6, Inostr. Lit., Moscow (1953), p. 98.
12. A. A. Akhrem, F. A. Lakhvich, S. I. Budai, T. S. Khlebanovich, and I. I. Petrusevich, Synthesis, No. 2, 925 (1978).
13. Japanese Patent 79 63,052; Chem. Abstr., **91,** 192911w (1979).
14. L. De Buyck, D. Seynaeve, and N. De Kimpe, Bull. Soc. Chim. Belg., **94,** 363 (1985).
15. E. V. Borisov and T. S. Khlebnikov, Dokl. Akad. Nauk Beloruss. SSR, **31,** 539 (1987).
16. W. F. Rowe, Jr., R. W. Duerst, and E. B. Wilson, J. Am. Chem. Soc., **98,** 4021 (1976).
17. A. J. Vila, C. M. Lagier, and A. C. Olivieri, J. Chem. Soc. Perkin Trans. 2, No. 16, 1615 (1990).
18. W. Winter, K.-P. Zeller, and S. Berger, Z. Naturforsch., **34b,** 1606 (1979).
19. R. Bible, Interpretation of Nuclear Magnetic Resonance Spectra [Russian translation], Atomizdat, Moscow (1969).
20. V. G. Avakyan, V. V. Gromak, and V. Z. Kurbako, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2377 (1989).