SYNTHESIS OF 12-MONO- AND DI-SUBSTITUTED 8-AZA-11-OXASTEROIDS

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ABSTRACT

The synthesis of unsaturated derivatives of 8-aza-11-oxa-17-oxo-gonane and D-homo-gonane carrying one or two functional substituents at C-12 is reported. The key step for the construction of the heterosteroid skeleton was the cyclocondensation reaction of aldol adducts **1**, derived from 1,3-cycloalkanediones and diethyl 2-oxo-malonate, with tosyl chloride and isoquinoline.

INTRODUCTION

The continuous interest in the field of heterosteroids mainly arises from the fascinating aspects associated with their peculiar stereochemical features and with their promising and sometime unexpected biological activities (1-5). Among the hundreds of nucleo-heterosteroids synthesized so far several 8-aza and 8-aza-16-oxasteroid derivatives have been claimed to possess good antiinflammatory, antifibrinolitic and membrane stabilizing activities (6). These observations prompted us to synthesize recently several derivatives of new heterosteroid ring systems, namely 8-aza-11-oxa- and 7,8-diaza-11--oxa-gonane and the corresponding D-homo-gonane, all containing either a 1,3-indanedione or a barbituric nucleus as a spiro-substituent at C-12 (7-10).

Unfortunately the pharmacological screening carried out on some selected lead compounds of the series to evaluate mainly endocrine, antiinflammatory, antimicrobial and CNS depressant activities, did not show any relevant results.

This fact in our opinion could however be ascribed to the high steric hindrance of the spiro-substituents and/or to the very low

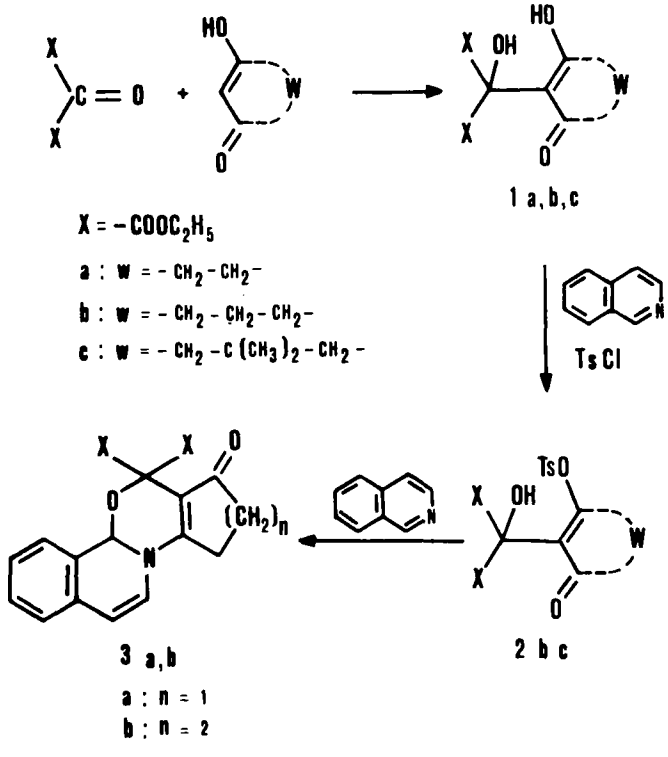
bioavailability very likely due to the poor solubility of the tested compounds in the physiological media.

We thus turned our attention to the synthesis of more soluble congeners lacking the bulky spiro-substituent at C-12; in this paper we wish to report the results obtained so far.

RESULTS AND DISCUSSION

Our goal has been achieved through the same synthetic route described previously (7-9), using as starting materials aldol adducts **1a,b,c**. The latter have been prepared from diethyl 2-oxo-malonate and 1,3-cycloalkanediones according to scheme I.

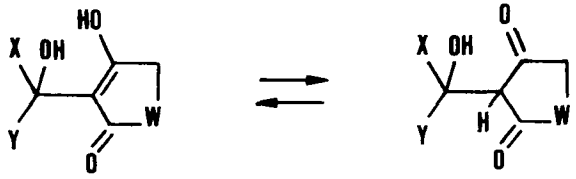
Scheme I



Our precedent studies on the dehydration of aldol adducts from 1,2,3-indanetrione had shown that most of those derived from acyclic CH-acid compounds easily underwent an elimination reaction yielding unsaturated polyoxo-derivatives (11), whereas those derived either from malonodialdehyde or from cyclic CH-acid compounds did not dehydrate (12). Fortunately adducts **1a-c**, potentially able to dehydrate upon treatment with tosyl chloride and isoquinoline, produced the desired 8-aza-11-oxasteroid derivatives **3a,b** and the enolic tosylate **2c** as outlined in scheme I.

Since we had observed that a condition for a prompt elimination reaction was the existence in solution of an appreciable amount of the ketonic form **1'** in the tautomeric equilibrium of aldol adducts **1** (Fig. 1) (11), the fact that in compounds **1a-c** no dehydration was observed could be due to their complete enolization, especially in the presence of weak heteroaromatic bases as can be seen from their ^{1}H-NMR spectra.

Fig. 1



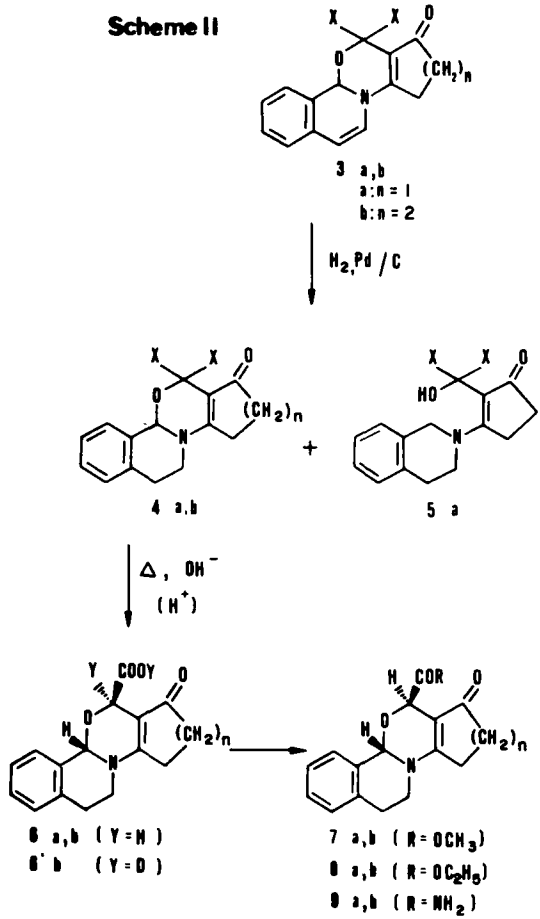
1 1

The different chemical behavior of compound **1c** leading to a stable tosylate intermediate **2c** is analogous to that observed in a similar reaction with pyridine (13) and could be ascribed to the strong steric

hindrance of the two geminal methyl groups which prevent the nucleophilic substitution by isoquinoline. On the other hand the tosylate **2b**, which could be isolated under the experimental conditions for which compound **1a** gave directly **3a**, reacted contrary to the tosylate **2c** with isoquinoline to give compound **3b**.

In order to increase the structural analogy with the skeleton of natural estrogens, oxa-azasteroids **3a-b** have been reduced under atmospheric pressure using Pd/C (5 %) as catalyst. The resulting products **4a.b** (scheme II) were obtained by the reduction of the Δ^6 double bond as shown by their analytical and spectroscopic properties (Table 3), fully consistent with those already reported by us for similar reduction products (10).

Scheme II



In the case of compound **1a**, when the reduction was carried out on a more concentrated catalyst (Pd/C, 10 %), the product **5a** arising from the hydrogenolysis of the C_9-O bond of derivative **4a**, could be isolated along with that product (**4a**).

The new oxa-azasteroid derivatives **4a,b**, although lacking the spiro-substituents, presented geminal groups at C-12 which could still create a certain steric hindrance in the eventual interactions at the receptor level. For this reason a decarboxylative hydrolysis has been undertaken with the aim of preparing a series of C-12 mono-substituted derivatives. In the experimental conditions chosen, the hydrolysis was highly stereoselective, yielding only diastereoisomeric acids **6a,b** in which the H-9 and the carboxylic group have a cis-diaxial configuration [Scheme II (14)].

This configurational assignment has been achieved by first determining the chemical shifts of H-9 and H-12 in compounds **6a,b** which presented two singlets at lower and higher field with respect to the H-9 signal in the corresponding starting products **4a,b**. Then the decarboxylative hydrolysis of diester **4b** was carried out in $NaOD/D_2O$ and the dideuterated acid **6'b** was obtained; its ^{1}H-NMR spectrum showed the H-9 singlet at δ=5.80 p.p.m., a value higher than that observed for the corresponding proton in ester **4b** (δ=5.46), and the persistence of a deshielding effect even stronger than in the latter product (**4b**) was ascribed to the carboxylic group in a cis-axial geometry with respect to the C-7 proton.

For a better evaluation of the influence of physico-chemical properties on eventual pharmacological activities of compounds **6**, we prepared the more hydrophobic methyl and ethyl esters **7a,b** and **8a,b** and the neutral and more hydrophilic primary amides **9a,b** [Scheme II (14)].

The 200 MHz NMR spectra of compounds **3-9** (Tables 2-4) have been tentatively interpreted on the basis of the 400 MHz spectral data reported by us for similar oxa-azasteroid derivatives carrying at C-12, instead of the bis-carbethoxy group, either a barbituric or a 1,3-indanedione moiety as the spiro-substituent (10).

A careful analysis of the data from B and D rings led to some interesting hypotheses about their preferred conformation(s) in solution.

The coupling constants J_{6-7} suggested that in compound **4a-b**, unlike compounds **6-9** and the C-12 spiro-substituted derivatives (10), the ring B should assume a "non-classical" chair conformation.

The coupling constants J_{15-16} and J_{16-17} and the small difference between the chemical shifts of the 16-protons in compounds **3** are consistent instead with an essentially "bisecting" character of 16-protons.

The above observations could be very useful in the evaluation of the results from binding studies at the receptor level, which have been already planned on some selected compounds reported in this paper.

EXPERIMENTAL

Melting points were determined by the capillary method on a Tottoli apparatus (Büchi) and were not corrected. Elemental analyses were made on a Hewlett-Packard 185 C,H,N analyzer and were in good agreement (±0.40 %) with calculated values. I R spectra were recorded using KBr disks on a Perkin-Elmer 283 spectrophotometer, only the most significant and diagnostic absorption bands being reported (NH, OH, CO and C=C stretchings). ^{1}H-NMR spectra were recorded in deuteriochloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6) on a Varian XL-200 spectrometer using TMS as internal standard, the following abbreviations being used: s, singlet; d, doublet; dd, double doublet; t, triplet; qt, quartet; qn, quintet; m, multiplet; br, broad signal. Exchange with deuterium oxide (D_2O) was used to identify hydroxyl protons. Chromatographic separations were carried out on silica gel columns (0.060-0.200 mm , Merck).

Preparation of diethyl 2-hydroxy-2-[2'-hydroxy-5'(6')-oxo-cycloalken-1'-yl] malonates **1a-c**

To a stirred ice-cooled solution of cyclic ß-diketone (cyclopentane-1,3-dione, cyclohexane-1,3-dione, dimedone) (9 mmol) in anhydrous ethanol (23 mL) was added dropwise a solution containing diethyl-2-oxo-malonate (1.567 g., 9 mmol) and sodium ethoxide (3.8 mmol) in the same solvent (25 mL). The reaction mixture was then allowed to warm to room temperature and stirred for 12 h. The solid residue, obtained after evaporation of the solvent in vacuo, was dissolved in 2N HCl (20 mL) and extracted with ethyl acetate. The organic layer was washed with water, dried on Na_2SO_4, evaporated to dryness and crystallized to give compound **1a** (75 % yield) m.p. 125-26°C, from ethyl acetate, compound **1b** (70 % yield) m.p. 74-76°C from ethyl ether, and compound **1c** (72 % yield) m.p. 103-105°C, from acetone. IR and ^{1}H-NMR data: Table 1.

Reaction of adducts **1a-c** with tosylchloride (TsCl)-isoquinoline

Title compounds **1** (4 mmol) and isoquinoline (2.583 g., 20 mmol) were dissolved in anhydrous dioxane (4 mL), and TsCl (838 mg, 4.4 mmol) was then added portionwise. The reaction mixture was stirred at room temperature for 14 h and poured on cold 2N HCl (16 mL). The resulting precipitate was collected, washed with water and dried to give:
from **1a**, 8-aza-11-oxa-12,12-bis(ethoxycarbonyl)-17-oxo-gona-1,3,5(10),6,13-pentaene **3a** (80 % yield) m.p. 173-174°C from chloroform-hexane, IR, ν_{max}: 1730,1690,1605,1560 cm^{-1}; from **1b**, after chromatographic separation on a silica gel column (80:20 ethyl acetate / hexane as eluant), diethyl 2-hydroxy-2-[6'-oxo-2'-tosyloxy-cyclohexen-1'-yl] malonate **2b** (50 % yield) m.p. 109-110°C, and 8-aza-11-oxa-12,12-bis(ethoxy-carbonyl)-17-oxo-D homogona-1,3,5(10),6,13 pentaene **3b** (30 % yield) m.p. 166-168°C, from chloroform-hexane: IR, ν_{max}: 1750,1740,1650,1635, 1590,1560 cm^{-1}. When the reaction mixture was carried out at 50°C with stirring for 15 h tosylate **2b** and oxazasteroid **3b** were obtained in 17 % and 63 % yield respectively: from **1c**: diethyl-2-hydroxy-2-[6'-oxo-2'-tosyloxy-4',4' dimethyl-cyclohexen-1'-yl] malonate **2c** (85 % yield) m.p. 99-100°C from chloroform-hexane. IR and ^{1}H-NMR data of compounds **2**: Table 1; ^{1}H-NMR data of compounds **3**: Table 2.

Reaction of diethyl-2-hydroxy-2-[6'-oxo-2'-tosyloxy-cyclohexen-1'-yl] malonate **2b** with isoquinoline

A mixture of tosylate **2b** (1.3 g, 2.95 mmol) and isoquinoline (5.3 g, 41.5 mmol) was heated at 45°C with stirring for 3 h and then poured on

ice-cold 2N HCl (80 mL). The resulting precipitate was collected, washed with water and dried to give oxazasteroid **3b** (75 % yield).

Preparation of 8-aza-11-oxa-12,12-bis-(ethoxycarbonyl)-17-oxo-gona--1,3,5(10),13-tetraene derivatives **4a,b** and diethyl 2-hydroxy-2-[2'--(1,2,3,4-tetrahydro-2-isoquinolyl)-5'-oxo-cyclopentenyl]-malonate **5a**

Oxazasteroids **3a,b** were reduced in dioxane solution under atmospheric pressure using Pd on carbon (5 %) as catalyst. The residue obtained after filtration of the catalyst and evaporation of the solvent solution in vacuo was purified by chromatography on a silica gel column (ethyl acetate as eluant) to give **4a** (90 % yield) m.p. 175-176°C from chloroform-hexane, IR, ν_{max}: 1740,1680,1595,1575 cm^{-1}; and **4b** (86 % yield) m.p. 98-99°C from ethyl ether-hexane, IR, ν_{max}: 1750,1740, 1645,1560 cm^{-1}. In the case of **3a**, when the reduction was carried out using Pd on carbon 10 % as catalyst, **4a** (32 % yield) and **5a** (48 % yield) m.p. 166-167°C from chloroform-hexane were obtained after chromatographic separation on a silica gel column (ethyl acetate as eluant). ^{1}H-NMR of compounds **4**: Table 3. **5a** IR, ν_{max}: 3460,1755,1725,1660,1590,1570 cm^{-1}; ^{1}H-NMR (chloroform-d) δ:1.24(t,6H,2CH_3-CH_2-OCO-,J=7.1), 2.28--2.34(m,2H, =C-CH_2-CH_2-).2.68-2.82(m,2H,=C-CH_2-CH_2-),2.92(t,2H,Ø-CH_2--CH_2-N-,J=5.9), 3.75(t,2H,Ø-CH_2-CH_2-N-,J=5.9), 4.04-4.34(m,4H,2-COO-CH_2 -CH_3), 4.63(s, 1H,OH,exch.D_2O), 4.70(s,2H,Ø-CH_2-N-), 6.98-7.24(m,4H, arom.,partially overlapped with the solvent signal).

Preparation of 8-aza-11-oxa-17-oxo-gona-1,3,5(10),13-tetraene-12-carboxylic acids **6 a,b**

Oxazasteroids **4** (6 mmol) were dissolved in ethanol (60 mL) and, after the addition of 10 % aqueous NaOH solution (12 mL), the reaction mixture was refluxed with stirring for 1 h. The solid residue obtained after evaporation of the solvent in vacuo was treated with cold 2N HCl (18 mL) to give **6a** (72 % yield) m.p. 223°C dec, from methanol, IR, ν_{max}: 2880br,2600br,1735,1565; or **6b** (83 % yield) m.p. 232°C dec., from propanol, IR, ν_{max}: 2800-2200,1730,1550 cm^{-1}. ^{1}H-NMR data: Table 3.

Preparation of 8-aza-11-oxa-17-oxo-gona-1,3,5(10),13-tetraene-12-carboxylic acids methyl esters **7a,b**

An ethereal solution of freshly prepared CH_2N_2 was added to a solution of carboxylic acid **7** (1 mmol) in anhydrous MeOH until a yellow, persistent color was obtained. The end of reaction was also

checked by TLC (ethyl acetate/methanol 90:10 as eluant). The solvent was then evaporated in vacuo and the solid residue crystallized to give **7a** (70 % yield) m.p. 198-200°C, from chloroform-hexane or **7b** (80 % yield) m.p. 115-117°C, from chloroform-hexane. IR and ^{1}H-NMR data:Table 4.

Preparation of 8-aza-11-oxa-17-oxo-gona-1,3,5(10),13-tetraene-12-carboxylic acid ethyl esters **8a,b**

A suspension of carboxylic acid **7** (1 mmol) absolute ethanol (0.27 mL) and p-toluenesulfonic acid (10 mg) in anhydrous benzene (3 mL) was refluxed under stirring for 6 h with azeotropic removal of the water. Then the reaction mixture was diluted with benzene (20 mL) and extracted twice with saturated $NaHCO_3$ solution (5 mL), washed with water and dried over Na_2SO_4. The solid residue obtained after evaporation of the solvent in vacuo was purified by chromatography on a silica gel column (90:10 ethyl acetate / chloroform as eluant) to give **8a** m.p. 160-162°C, from chloroform-hexane or **8b** m.p. 125-127°C, from ethyl ether in 78 % and 80 % yield respectively. IR and ^{1}H-NMR data: Table 4.

Preparation of 8-aza-11-oxa-17-oxo-gona-1,3,5(10),13-tetraene-12-carboxylic acid amides **9a,b**

Methyl ester **7** (0.3 mmol) was added to 30 % NH_3 (2 mL). After a week the muddy reaction mixture was filtered and the precipitate washed with water and crystallized from chloroform-hexane to give **9a** m.p. 215°C dec. or **9b** m.p.220°C dec. in 70 % and 72 % yield respectively. IR and ^{1}H-NMR data: Table 4.

TABLE 1 - SPECTROSCOPIC DATA OF ALDOL ADDUCTS 1 AND INTERMEDIATE TOSYLATES 2b,c

Compound	I R KBr disks ν_{max}, cm^{-1}	^{1}H-NMR, $CDCl_3$ δ(ppm), J(Hz)
1a	3430,2700-2200, 1745,1730,1580,1560	1.30(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1); 2.20-2.85(m,4H,-CH_2-CH_2-); 5.50-7.90(br,1H,alcoholic-OH,exch.D_2O); 4.30(qt,4H, -COO-$\underline{CH_2}$-CH_3,J=7.1); 10.45-12.30(br,1H,enolic-OH,exch.D_2O)
1b	3400 br,3220 br, 2700-2200, 1750,1725,1595	ketonic form (~65 %): 1.27(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1); 1.70-2.02(m,2H,-CH_2-$\underline{CH_2}$-CH_2-); 2.52-2.82(m,4H,2-C(=O)-CH_2-); 4.04(s,1H,-OH,exch.D_2O); 4.26(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.29(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.75(s,1H,-CH-,exch.D_2O)
		[a] enolic form (~35 %): 1.27(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1); 2.06-2.28(m,2H,-CH_2-$\underline{CH_2}$-CH_2-); 2.30-2.50(m,2H,-C=C-CH_2-); 4.04(s,1H,-OH,exch.D_2O); 4.26(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.29(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); signals of the other -CH_2- group were masked by the -$\underline{CH_2}$- signals of the ketonic form at 2.52-2.82; the signal due to the enolic -OH is not easily detectable
1c	3470,2700-2200, 1730,1555	ketonic form (~85 %): 0.83(s,3H,-C-CH_3); 1.16(s,3H,-C-CH_3); 1.27(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1); 2.44-2.70(AB systems, 4H,CH_2-C-CH_2,partially overlapped with the signals of the corresponding protons of the enolic form); 4.03(s,1H,-OH,exch.D_2O); 4.25(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.27(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.65(s,1H,-CH-,exch.D_2O)
		enolic form (~15 %): 1.05(s,6H,2-C-CH_3);1.27(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1);2.30(s,2H,-C=C-CH_2);2.51(s,2H,-C(=O)-CH_2-, masked by the signals of AB system of the ketonic form); 4.03(s,1H,-OH,exch.D_2O);4.25(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.27(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); the signal due to the enolic -OH is not easily detectable
2b	3450 1750,1730,1680,1630	1.19(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7.1); 2.03(qn,2H,-CH_2-$\underline{CH_2}$-CH_2-,J=6.3); 2.41(t,2H,C=C-CH_2-,J=6.3); 2.45(s,3H,-Ø-CH_3, partially overlapped with the CH_2- signal);2.92(t,2H,-C(=O)-CH_2-,J=6.3); 3.50(br,1H,-OH,exch.D_2O); 4.11(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 4.13(qt,2H,-COO-$\underline{CH_2}$-CH_3,J=7.1); 7.30-7.92(A_2B_2 system,4H,Arom)
2c	3450 1750,1730,1675,1625	1.07(s,6H,2-C-CH_3); 1.18(t,6H,2$\underline{CH_3}$-CH_2-OCO-); 2.28(s,2H,-C=C-CH_2-); 2.45(s,3H,Ø-CH_3); 2.81(s,2H,-C(=O)-CH_2); 3.56(br,1H,-OH,exch.D_2O); 4.10(qt,2H,-COO-$\underline{CH_2}$-CH_3); 4.12(qt,2H,-COO-$\underline{CH_2}$-CH_3); 7.30-7.92(A_2B_2 system,4H,Arom)

a) After addition of a few drops of pentadeuteropyridine only the following signals due to the enolate anion of **1b** are detected in the ^{1}H-NMR spectrum ($CDCl_3$): 1.23(t,6H,2$\underline{CH_3}$-CH_2-OCO-,J=7); 1.95(qn,2H,-CH_2-$\underline{CH_2}$-CH_2-,J=6); 2.50(t,4H,-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-,J=6); 4.23(qt,4H,2-COO-$\underline{CH_2}$-CH_3,J=7); 6.63(br,2H,exch. D_2O).

TABLE 2 - ^{1}H-NMR OF 8-AZA-11-OXA-17-OXO-GONA- AND D-HOMO-GONA-1,3,5(10),6,13-PENTAENE DERIVATIVES 3a,b[a]

	3a			3b		
Protons	Mt[b]	δ,ppm	J (Hz)	Mt[b]	δ,ppm	J (Hz)
1	m	7.73-7.77		m	7.65-7.69	
2, 3	m	7.27-7.31		m	7.24-7.30	
4	m	7.03-7.08		m	7.01-7.06	
6	d	5.77	7.7	d	5.75	8.0
7	d	6.48	7.7	d	6.60	8.0
9	s	6.32		s	6.19	
15 ax	2dd	2.48	18.0 (gem)	2dd	2.38	16.5 (gem)
			7.6 (aa)			6.6 (aa)
			4.3 (ae)			5.0 (ae)
15 eq	2t	2.59	4.5 (ea)	2t	2.52	6.0 (ea)
			4.5 (ee)			6.0 (ee)
16 ax[d]	2dd	2.76	17.6 (gem)	m	2.05-2.17	
16 eq[d]	2t	2.88				
17 ax				2dd	2.60	17.6 (gem)
						7.1 (aa)
						5.5 (ae)
17 eq				2t	2.77	6.2 (ea)
						6.2 (ee)
-CO-O-$\underline{CH_2}$-CH_3	qt	4.26	7.1	qt	4.24	7.1
	qt[c]	4.36	7.1	qt[c]	4.33	7.1
-CO-O-CH_2-$\underline{CH_3}$	t	1.27	7.1	t	1.27	7.1
	t	1.34	7.1	t	1.35	7.1

a) Spectra were recorded in $CDCl_3$. b) Mt = multiplicity; for abbreviations see at the beginning of the section "Experimental". Coupling constants and multiplicity have been listed only where clearly determinable. c) Sometimes observed as double quartet. d) 16-protons, practically "bisecting" (see text), have been designed as "ax" and "eq" only for the table homogeneity.

TABLE 3 - ^{1}H-NMR OF 8-AZA-11-OXA-17-OXO-GONA- AND D-HOMO-GONA-1,3,5(10),13-TETRAENE DERIVATIVES 4a,b AND 6a,b[a]

	4a ($CDCl_3$)			4b ($CDCl_3$)			6a (DMSO-d_6)			6b (DMSO-d_6)		
Protons	Mt[b]	δ, ppm	J (Hz)	Mt[b]	δ, ppm	J (Hz)	Mt[b]	δ, ppm	J (Hz)	Mt[b]	δ, ppm	J (Hz)
1	m	7.74-7.78		m	7.71-7.75		dd	7.55	5.4 (o) 3.6 (m)	dd	7.58	9.1 (o) 3.6 (m)
2 3	m	7.29-7.34		m	7.24-7.31		m	7.24-7.35		m	7.22-7.37	
4	m	7.13-7.17		m	7.10-7.15							
6 ax	2dd	3.11	15.8 (gem) 8.8 (aa) 5.0 (ae)	2dd	3.03	15.8 (gem) 8.0 (aa) 4.5 (ae)	2dd	3.00	12.5 (gem) 9.2 (aa) 5.3±0.3 (ae)	2dd	2.96	16.3 (gem) 8.3 (aa) 5.1 (ae)
6 eq	2t	2.83	4.7 (ea) 4.4±0.3 (ee)	2dd	2.80	6.3 (ea) 4.4 (ee)	2t	2.84	4.7 (ea) 5.0 (ee)	2t	2.79	4.5 (ea) 5.1 (ee)
7 eq	2t	3.74	12.4 (gem)	2dd	3.69	12.5 (gem)	2t	3.73	13.0 (gem)	2t	3.80	12.9 (gem)
7 ax	2dd	3.57		2dd	3.51		2dd	3.59		2dd	3.57	
9	s	5.63		s	5.46		s	5.76		s	5.80	
12							s	5.05		s	5.19	
15 ax	2dd	2.43	14.1 (gem) 7.6±0.9 (aa) 4.2 (ae)	m	2.24-2.38		2t[c]	1.49	10.0 (gem)	m	2.28-2.35	
15 eq	2t	2.54	4.7 (ea) 4.7 (ee)				2t[c]	1.60	6.0 (aa) 6.0 (ae)			
16 ax	2dd	2.69	17.8 (gem)	m	2.01-2.11		m	2.23-2.35		m	1.80-1.98	
16 eq	2t	2.78										
17 ax				2dd	2.60	15.4 (gem) 9.5 (aa) 3.3 (ae)				m	2.53-2.66[d]	
17 eq				m[f]	2.60-2.75							
-CO-O-$\underline{CH}_2$-CH_3	qt	4.25	7.1	qt[e]	4.23	7.1						
	qt[e]	4.36	7.1	qt[e]	4.31	7.1						
-CO-O-CH_2-$\underline{CH}_3$	t	1.26	7.1	t	1.26	7.1						
	t	1.34	7.1	t	1.32	7.1						

Notes: see following page.

TABLE 3 - Notes:
a)Spectra were recorded in the solvents indicated in parentheses using TMS as internal standard.b)Mt=multiplicity;for abbreviations see at the beginning of the section "Experimental." Coupling constants and multiplicity have been listed only where clearly determinable.c)Assignment of the two signals can also be reversed.d)Partially masked by DMSO-d_6 signals.e)Sometimes observed as double quartet.f)Partially overlapped with H-17ax and H-6eq signals.

TABLE 4 - SPECTROSCOPIC DATA OF CARBOXYLIC ACID DERIVATIVES 7, 8, 9

Compound	I R KBr disks νmax, cm^{-1}	^{1}H-NMR, CDCl$_3$ δ(ppm), J(Hz)
7a	1740,1660,1590 1570	2.38-2.60(m,2H,H-15ax and H-15eq); 2.64-2.84(m,2H,H-16ax and H-16eq); 2.85-3.14(m,2H,H-6ax and H-6eq);3.56-3.80(m,2H, H-7ax and H-7eq);3.80(s,3H,$\underline{CH}_3$-OCO);5.24(s,1H,H-12);6.03(s,1H,H-9); 7.00-7.46(m,3H,H-2 + H-3 + H-4); 7.53-7.80(m,1H,H-1)
7b	1730,1620,1560	1.98-2.18(m,2H,H-16ax and H-16eq); 2.26-2.54(m, 2H,H-15ax and H-15eq); 2.58-2.72(m,2H,H-17ax and H-17eq); 2.84(2t,1H, H-6eq,Jgem=16.0,Jea=Jee=5.0); 3.04(2dd,1H,H-6ax,Jgem=16.0,Jaa=8.0,Jae=5.0); 3.56(2dd,1H,H-7ax,Jgem=12.4,Jaa=8.0,Jae=5.0); 3.72(2t,1H,H-7eq,Jgem=12.4,Jea=Jee=5.0); 3.84(s,3H,$\underline{CH}_3$-OCO-); 5.32(s,1H,H-12); 5.92(s,1H,H-9); 7.10-7.20(m,1H,H-4); 7.26-7.40(m,2H,H-2 + H-3); 7.50-7.58(m,1H,H-1)
8a	1735,1665,1610 1595,1580	1.32(t,3H,$\underline{CH}_3$-CH_2-OCO-,J=7.1); 2.32-2.64(m,2H,H-15ax and H-15eq); 2.70-2.80(m,2H,H-16ax and H-16eq); 2.84(2t,1H,H-6eq, Jgem=16.0,Jea=Jee=4.0); 3.07(2dd,1H,H-6ax,Jgem=16.0,Jaa=8.0,Jae=4.0); 3.58(2dd,1H,H-7ax,Jgem=12.0,Jaa=8.0,Jae=4.0); 3.74(2t,1H,H-7eq,Jgem=12.0,Jea=Jee=4.0); 4.27(qt,2H,CH_3-$\underline{CH}_2$-OCO-,J=7.1); 5.21(s,1H,H-12); 6.01(s,1H,H-9); 7.14-7.18(m,1H, H-4); 7.26-7.34(m,2H,H-2 + H-3); 7.65-7.69(m,1H,H-1)
8b	1730,1620,1590, 1570	1.35(t,3H,$\underline{CH}_3$-CH_2-OCO-,J=7.1); 1.96-2.10(m,2H,H-16ax and H-16eq); 2.12-2.44(m,2H,H-15ax and H-15eq); 2.47-2.71(m,2H, H-17ax and H-17eq); 2.84(2t,1H,H-6eq,Jgem=16.0,Jea=Jee=5.0); 3.02(2dd,1H,H-6ax,Jgem=16.0,Jaa=8.0,Jae=4.6); 3.55(2dd,1H, H-7ax,Jgem=12.4,Jaa=8.0,Jae=4.2); 3.70(2t,1H,H-7eq,Jgem=12.4,Jea=Jee=6.0); 4.28(qt,2H,CH_3-$\underline{CH}_2$-OCO,J=7.1); 5.26(s,1H, H-12); 5.87(s,1H,H-9); 7.14-7.19(m,1H,H-4); 7.28-7.36(m,2H,H-2 + H-3); 7.50-7.55(m,1H,H-1)
9a	3300br,3150br, 1695,1570	2.52(t,2H,H-15ax and H-15eq, Jae=Jee=4.8); 2.74-2.84(m,2H,H-16ax and H-16eq); 2.84(2t,1H,H-6eq,Jgem=16.0,Jea=Jee=5.0); 3.01(2dd,1H,H-6ax,Jgem=16.0,Jaa=8.0,Jae=4.0); 3.62(2dd,1H,H-7ax,Jgem=12.4,Jaa=8.0,Jae=5.0); 3.75(2t,1H,H-7eq,Jgem=12.4, Jea=Jee=5.0); 5.12(s,1H,H-12); 5.48(br,1H,-$\underline{NH}_2$,exch.D_2O); 5.82(s,1H,H-9); 7.12-7.16(m,1H,H-4); 7.25-7.39(m,2H,H-2 + H-3); 7.82(br,1H,-$\underline{NH}_2$,exch.D_2O); 7.83-7.90(m,1H,H-1)
9b	3360br,3180br, 1685,1540	1.95-2.09(m,2H,H-16ax and H-16eq); 2.36-2.43(m,2H,H-15ax and H-15eq); 2.59(t,2H,H-17ax and H-17eq,Jae=Jee=6.4);2.81(2t, 1H,H-6eq,Jgem=16.0,Jea=Jee=4.5);3.01(2dd,1H,H-6ax,Jgem=16.0,Jaa=8.7,Jae=4.0);3.52(2dd,1H,H-7ax,Jgem=12.7,Jaa=8.7, Jae=4.0); 3.78(2t,1H,H-7eq,Jgem=12.7,Jea=Jee=4.5); 5.36(s,1H,H-12); 5.46(br,1H,-$\underline{NH}_2$,exch.D_2O); 6.29(s,1H,H-9); 7.10-7.14(m,1H,H-4); 7.23-7.36(m,2H,H-2 + H-3); 7.82-7.87(m,1H,H-1); 7.93(br,1H,-$\underline{NH}_2$,exch.D_2O)

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14. Only one enantiomer of the racemic mixtures of compounds **6,7,8,9** is shown, for simplicity, in the scheme.