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^{13}C NMR SPECTRA OF A NUMBER OF PENTA- AND HEXACYCLIC TRITERPENOIDS DERIVED FROM GLYCYRRHETIC ACID

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The ^{13}C NMR spectra of 22 derivatives of 18α- and 18β-glycyrrhetic acids that have been investigated and an assignment of the signals has been made. It has been shown that a modification of the carboxy group of glycyrrhetic acid leads mainly to a change in the chemical shifts of the α-, β-, and γ-carbon atoms of ring E. The assignment of a number of signals has been confirmed by the use of the shift reagent Eu(fod)$_3$. It has been established that the C_{28} and C_{16} signals are the most sensitive to a change in the C_{18} configuration in the spectra of glycyrrhetic acid derivatives.

The high and varied biological activity of glycyrrhetic acid and its derivatives is arousing the interest of chemists in synthetic transformations of this acid connected with the modification both of the functional groups and of the carbon skeleton itself.

The most informative method of studying the structure of polycyclic compounds is ^{13}C NMR spectroscopy [1]. There are only two publications, by Ricca et al. [2, 3], on the ^{13}C NMR spectra of glycyrrhetic acid derivatives. These authors investigated and interpreted the ^{13}C NMR spectra of a number of derivatives of 18α- and 18β-glycyrrhetic acids and their 11-deoxo analogs, made an assignment of the signals, and showed that the configuration of the isomers at C_{18} can be determined from the chemical shifts (CSs) of a number of characteristic carbon atoms (C_{12}, C_{13}, C_{18}, C_{28}), the positions of the signals of which depend on the type of linkage of the D/E rings.

Using various methods, we have synthesized a number of derivatives of 18α- and 18β-glycyrrhetic acids (I-XXII) and have studied their ^{13}C NMR spectra.

Table 1 gives the values of the CSs and the multiplicities of the signals obtained from spectra with off-resonance proton suppression for the 18α- and 18β-glycyrrhetic acid derivatives investigated.

The spectra of compounds (I-IV and XVI-XVIII) practically coincided with those given in the literature [2, 3]. We are the first to have recorded and interpreted the ^{13}C NMR spectra of the other compounds.

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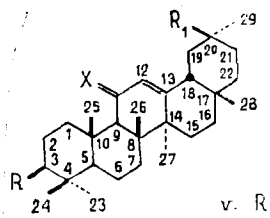
TABLE 1. Chemical Shifts and Multiplicities of the ^{13}C NMR Signals of Glycyrrhetic Acid Derivatives (δ, ppm, $CDCl_3$, DMFA-d_7*; s — singlet; d — doublet; t — triplet; q — quartet)

C atom	I	II	III	IV*	V	VI	VII	VIII	IX	X	X+Eu(fod)$_3$	$\Delta\delta$	XI
C_1	39,11 t	39,13 t	38,71 t	39,18 t	38,77 t	38,77 t	38,77 t	38,77 t	38,55 t	40,93 t	41,65	0,72	37,80 t
C_2	27,12 t	27,29 t	23,50 t	23,96 t	23,57 t	23,53 t	23,53 t	23,53 t	23,53 t	18,44 t	18,67	0,23	23,43 t
C_3	78,44 d	78,69 d	80,55 d	78,07 d	80,55 d	80,52 d	80,58 d	80,62 d	80,42 d	42,01 t	42,17	0,16	80,55 d
C_4	39,11 s	39,13 s	37,99 s	39,26 s	38,02 s	38,02 s	38,02 s	38,02 s	37,80 s	33,36 s	33,68	0,32	38,15 s
C_5	54,93 d	54,93 d	54,96 d	55,98 d	54,99 d	54,99 d	54,99 d	54,99 d	54,93 d	55,68 d	56,01	0,33	54,70 d
C_6	17,47 t	17,49 t	17,33 t	18,90 t	17,36 t	17,36 t	17,40 t	17,36 t	18,21 t	17,72 t	18,02	0,30	17,78 t
C_7	32,75 t	32,77 t	32,64 t	33,16 t	32,67 t	32,67 t	32,70 t	32,70 t	32,74 t	32,77 t	32,96	0,19	33,18 t
C_8	43,20 s	43,18 s	43,15 s	40,31 s	43,11 s	43,18 s	43,28 s	43,38 s	43,37 s	43,18 s	43,54	0,36	42,66 s
C_9	61,77 d	61,82 d	61,65 d	47,20 d	61,75 d	61,72 d	61,67 d	61,75 d	45,73 d	61,91 d	61,69	0,22	63,35 d
C_{10}	37,07 s	37,08 s	36,88 s	37,15 s	36,95 s	36,91 s	36,91 s	36,91 s	34,17 s	37,34 s	37,86	0,52	36,72 s
C_{11}	200,43 s	200,17 s	199,94 s	30,21 s	199,71 s	199,61 s	199,75 s	200,43 s	70,43 d	200,43 s	202,79	2,35	208,85 s
C_{12}	128,40 d	128,50 d	128,37 d	122,59 d	128,79 d	128,56 d	128,43 d	128,01 d	121,19 d	128,60 d	130,23	1,63	44,64 t
C_{13}	169,49 s	169,13 s	169,23 s	145,47 s	167,73 s	168,06 s	168,61 s	170,11 s	150,49 s	168,74 s	170,50	1,76	132,71 s
C_{14}	45,45 s	45,37 s	45,33 s	42,17 s	45,37 s	45,37 s	45,40 s	45,50 s	41,55 s	45,63 s	46,22	0,59	37,80 s
C_{15}	26,40 t	26,44 t	26,37 t	27,65 t	26,40 t	26,31 t	26,37 t	26,21 t	26,76 t	26,44 t	26,57	0,13	25,69 t
C_{16}	26,40 t	26,44 t	26,37 t	26,65 t	26,34 t	26,18 t	26,27 t	26,21 t	26,21 t	26,44 t	26,57	0,13	25,69 t
C_{17}	31,85 s	31,82 s	31,79 s	32,86 s	31,92 s	31,86 s	31,86 s	31,82 s	31,99 s	31,82 s	31,99	0,17	34,62 s
C_{18}	48,17 d	48,37 d	48,34 d	48,17 d	47,75 d	47,23 d	46,67 d	46,57 d	52,12 d	48,37 d	48,57	0,20	132,28 s
C_{19}	40,86 t	41,09 t	41,03 t	42,69 t	41,48 t	44,49 t	41,92 t	43,18 t	42,07 t	41,09 t	41,45	0,36	36,13 t
C_{20}	43,79 s	44,03 s	43,96 s	57,25 s	54,38 s	58,58 s	52,38 s	52,61 s	37,93 s	44,03 s	44,32	0,29	44,19 s
C_{21}	30,90 t	31,14 t	31,07 t	30,21 t	31,56 t	34,80 t	31,86 t	30,48 t	29,73 t	31,14 t	31,33	0,19	32,83 t
C_{22}	37,70 t	37,73 t	37,70 t	39,20 t	37,11 t	36,20 t	35,58 t	35,94 t	36,29 t	37,76 t	38,25	0,49	36,13 t
C_{23}	28,07 q	28,10 q	28,00 q	27,83 q	28,04 q	28,04 q	28,07 q	28,07 q	27,97 q	33,57 q	33,68	0,11	28,00 q
C_{24}	15,61 q	15,60 q	16,64 q	15,80 q	16,68 q	16,68 q	16,68 q	16,68 q	16,45 q	21,81 q	22,00	0,16	16,68 q
C_{25}	16,36 q	16,38 q	16,35 q	16,29 q	16,38 q	16,38 q	16,38 q	16,38 q	17,20 q	16,29 q	17,04	0,75	16,32 q
C_{26}	18,68 q	18,67 q	18,64 q	18,80 q	18,67 q	18,67 q	18,70 q	18,63 q	18,21 q	18,77 q	19,13	0,36	18,80 q
C_{27}	23,39 q	23,40 q	23,30 q	23,96 q	23,37 q	23,30 q	23,30 q	23,24 q	25,46 q	23,40 q	23,89	0,49	23,92 q
C_{28}	28,43 q	28,33 q	28,26 q	28,26 q	28,30 q	28,17 q	28,20 q	28,07 q	27,97 q	28,33 q	28,53	0,20	19,68 q
C_{29}	28,53 q	28,53 q	28,49 q	28,56 q	27,38 q	31,69 q	28,30 q	28,49 q	28,20 q	28,49 q	28,53	0,04	28,00 q
C_{30}	181,53 s	176,87 s	176,83 s	65,54 t	179,02 s	122,20 s	155,32 s	155,68 s	67,72 t	176,83 s	176,89	0,06	178,60 s
C_{31}		51,76 q	51,70 q		170,86 s	170,83 s	51,60 q	139,53 s	171,18 s	51,70 q	51,90	0,20	51,79 q
C_{32}			170,86 s		21,28 q	21,25 q	170,93 s	119,62 d	20,89 q				170,93 s
C_{33}			21,25 q				21,28 q	128,95 d	170,93 s				21,28 q
C_{34}								122,55 d	21,28 q				
C_{35}								171,03 s	170,93 s				
C_{36}								21,08 q	21,87 q				

The assignment of the signals in the spectra of the glycyrrhetic acid derivatives was made on the basis of literature information for the model compounds (I-IV and XVI-XVIII) [2, 3], and also in accordance with the characteristic shifts of the signals of the functional groups and the multiplicities of the signals obtained from spectra with partial proton suppression.

Thus, the C_{30} carboxy group in the spectrum of glycyrrhetic acid (I) gives a signal at 181.53 ppm, and the CSs of the carbonyl carbon atom of the methyl esters (II) and (III) have values of ~176 ppm. The C_{30} hydroxymethyl group in the spectrum of compound (IV) appears in the form of a triplet at 65.54 ppm, and the CS of the carbonyl chloride group in the spectrum of the acid chloride (V) occupies an intermediate position between the CSs of the carbonyl atoms of the C_{30} acid (I) and of the methyl esters (II) and (III). The isocyanate group in the spectrum of compound (VI) is revealed from the singlet signal at 122.20 ppm. For comparison we can give the corresponding signal δ_{NCO} = 123.60 ppm for cyclohexyl isocyanate [5]. In the spectra of the other nitrogen-containing compounds (VII) and (VIII), the signal of the C_{30} is observed in the 155-158 ppm region.



I. R = OH, $R_1 = \overset{30}{C}OOH$, X = O;

II. R = OH, $R_1 = \overset{30}{C}OO\overset{31}{C}H_3$, X = O;

III. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{C}OO\overset{31}{C}H_3$, X = O;

IV. R = OH, $R_1 = \overset{30}{C}H_2OH$, $X = H_2$;

V. R = $\overset{31}{O}C\overset{32}{O}CH_3$, $R_1 = \overset{30}{C}OCl$, X = O;

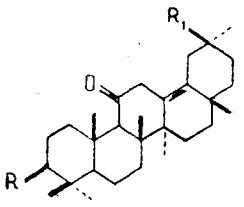
VI. R = $\overset{31}{O}C\overset{32}{O}CH_3$, $R_1 = \overset{30}{N}CO$, X = O;

VII. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{N}H\overset{31}{C}OOCH_3$, X = O;

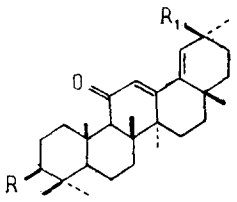
VIII. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = NHCONHC_6H_5$, X = O;

IX. R = $\overset{33}{O}C\overset{34}{O}CH_3$, $R_1 = \overset{30}{C}H_2\overset{31}{O}C\overset{32}{O}CH_3$, X = $\overset{35}{O}C\overset{36}{O}CH_3$;

X. R = H_2, $R_1 = COO\overset{31}{C}H_3$, X = O



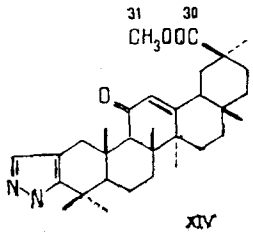
XI



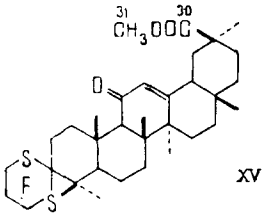
XII. R = OH, $R_1 = \overset{30}{C}OOH$

R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{C}OO\overset{31}{C}H_3$

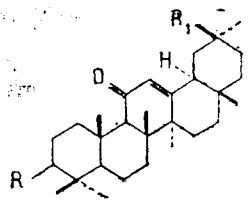
XIII. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{C}OO\overset{31}{C}H_3$



XIV



XV



XVI. R = OH, $R_1 = \overset{30}{C}OOH$;

XVII. R = $\overset{31}{O}C\overset{32}{O}CH_3$, $R_1 = \overset{30}{C}OOH$;

XVIII. R = OH, $R_1 = \overset{30}{C}OO\overset{31}{C}H_3$;

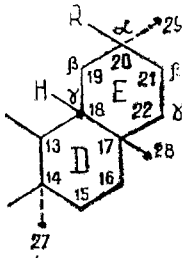
XIX. R = $\overset{31}{O}C\overset{32}{O}CH_3$, $R_1 = \overset{30}{N}CO$;

XX. R = $\overset{31}{O}C\overset{32}{O}CH_3$, $R_1 = \overset{30}{C}OCl$;

XXI. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{N}H\overset{31}{C}ONHC_6H_5$;

XXII. R = $\overset{32}{O}C\overset{33}{O}CH_3$, $R_1 = \overset{30}{N}H\overset{31}{C}OOCH_3$

TABLE 2. Increments of the CSs of the Functional Groups at C_{20} Relative to the Carboxy Group of 18β-Glycyrrhetic Acid, $\Delta_N = \delta C_{iN} - \delta C_{iI}$



Carbon	$\delta_{II}-\delta_I$	$\delta_{VI}-\delta_I$	$\delta_V-\delta_I$	$\delta_{VII}-\delta_I$	$\delta_{IX}-\delta_I$
C_{13}	−0.36	−1.40	−1.76	−1.88	+0.62
C_{17}	−0.03	+0.01	+0.07	+0.14	+0.03
C_{18}	+0.20	−0.94	−0.42	+3.95	+1.60
C_{19}	+0.13	+3.63	+0.62	+1.21	+2.32
C_{20}	+0.24	+14.79	+10.59	+8.59	+8.52
C_{21}	+0.24	+3.90	+0.66	−1.17	−0.42
C_{22}	+0.03	−1.50	−0.59	−1.41	−1.76
C_{29}	0	+3.16	−1.15	−0.33	−0.04

It is known that the introduction of a functional group (or the replacement of one functional group by another) leads in ^{13}C NMR spectra to changes in the CSs of the neighboring α-, β-, and γ- (and sometimes even δ-) -carbon atoms [5]. Consequently, in the case of compounds (II) and (V-VIII) in which the carboxy group (C_{30}) has been replaced by other functions, one should expect changes in the CSs of the signals of the carbon atoms of rings D and E.

In actual fact, the replacement of the COOH group (C_{30}) by COCl, NCO, $NHCO_2CH_3$, and NHCONHPh functions led mainly to changes in the CSs of the α-, β-, and γ-carbon atoms. Table 2 gives the α-, β-, γ-, and δ- increments of these functional groups relative to the carboxy group of glycyrrhetic acid.

Thus, replacement of the carboxy group of the glycyrrhetic acid molecule by an acid chloride group in compound (V) led to downfield shifts of 10 ppm for the signal of the C_{20} atom, in contrast to the ester group in derivatives (II) and (III), which is characterized by the differences in the α-increments of the COOH, COOMe, and COCl groups [4].

Nitrogen-containing groups (NCO, $NHCO_2CH_3$, and NHCONHPh) also exert a considerable descreening influence on the shift of the C_{20} signal amounting to 14-15 ppm in the case of the isocyanate (VI) and to about 8 ppm for compounds (VII and VIII).

The β-effect in compounds (V-VIII) appears mainly on C_{19} and leads in all cases to a downfield shift of the signals of this carbon atom by 0.62-3.63 ppm in comparison with the corresponding signals of 18β-glycyrrhetic acid (I). The isocyanate group in compound (VI) also exerts an appreciable descreening influence on the C_{21} signal (of about 4.0 ppm).

Nitrogen-containing functional groups exert a small screening effect (of about 2 ppm) on the γ-carbon atoms of ring E (C_{22}). In derivatives (II) and (III), the carbon atoms of ring A, B, and C are practically insensitive to a change in the function at C_{20}.

The replacement of the carbonyl group at C-11 by an acetoxy group in compound (IX) leads to a doubling of the intensity of the signal at 170.93 ppm (C_{35}) and to the appearance of a quartet signal at 21.87 ppm (C_{36}).

The upfield shift of the C_9 signal of 6 ppm (45.73 ppm) is due to the weak effect of the acetoxy group as compared with the contribution of the carbonyl group in compounds (I-VIII).

The signals of the C_{12} and C_{13} double-bond atoms shift upfield in comparison with the corresponding signals of the conjugated systems (I-VIII) because of the absence of conjugation with the carbonyl group.

The elimination of the β-hydroxy group at C_3 in compound (X) leads to an upfield shift of the C_3 signal to 42.01 ppm (Δ 36.43 ppm). The C_3 signal in the spectrum of the deoxy derivative (X) appears in the form of a triplet in the spectrum with partial decoupling from protons. For this compound, in order to confirm and refine the assignment of the signals, we recorded the spectra with the addition of the shift reagent $Eu(fod)_3$ [6]. Table 1 gives the CSs and the induced CSs (ICSs) for the maximum addition

$$\Delta ICS_i = \delta C_{iEu+X} - \delta C_{iX}.$$

The highest ICS values are observed for the C_{11} carbonyl carbon atom and its closest environment. The inconsiderable shifts of the signals of the ester group R_1 permit the statement that there is practically no complex-formation with the lanthanoid reagent at this group, and this takes place only at the C_{11} carbonyl group.

The ICSs confirm the assignment of the C_8, C_{10}, and C_{14} singlet signals, the C_1 triplet signal, and the quartet signals of the C_{25}, C_{26}, and C_{27} methyl groups. However, the diamagnetic shift of the C_9 signal at a distance of two bonds from the carbonyl atom causes certain difficulties in the unambiguous interpretation of the ICSs [7]. The assignment of the C_9 signal was confirmed by modifying the carbonyl function in position 11 (compounds IV and IX).

Skeletal transformations of the glycyrrhetic acid molecule cause more substantial changes in the spectra. Thus, the presence of an isolated double bond in the C_{13}—C_{18} position in compound (XI) leads to the appearance of C_{13} and C_{18} singlet signals at 132.28 and 132.78 ppm. The flattening of ring D through the introduction of a double bond leads to the degeneracy of the isomers with respect to position 18. The signal of the C_{28} atom then occupies an intermediate position (19.68 ppm) between the extreme values δC_{28} (I) = 28.45 ppm for the β-series and δC_{28} (XV) = 16.15 ppm for the α-series. The diamagnetic nature of the shift of the signal in comparison with the corresponding signals of the β-series is due to the presence of one additional γ-gauche interaction of the C_{28} methyl group with the axial proton at C_{21}.

The introduction into the glycyrrhetic acid molecule of another double bond at C_{18} (compound XII) leads to the appearance in the spectrum of additional signals in the region of olefinic carbon atoms: a singlet at 142.92 ppm (C_{18}) and a doublet at 124.06 ppm (C_{19}).

Considerable changes take place in the spectrum on the introduction of a sixth, heterocyclic, ring F into the triterpenoid molecule (compounds XIV and XV). Thus, the introduction of a pyrazole ring into compound (XIV) is accompanied by the appearance of three additional signals in the region of unsaturated carbon atoms. Two singlet signals at 148.47 and 112.08 ppm are assigned to the C_2 and C_3 sp^2-hybridized carbon atoms shared with ring A, respectively. A doublet signal at 134.17 ppm belongs to ring F itself. The presence of a pyrazole ring also leads to an upfield shift of the signals of the C_{23} methyl group by 4 ppm in comparison with the corresponding signal of a model compound — for example, (II). A corresponding contribution to the screening of C_{23} is made by a γ-gauche interaction with the proton of the C_{10} methine carbon atom.

The signals of the C_1, C_4, and C_5 carbon atoms of ring A, and also those of the C_{25} methyl group, are shifted upfield by 1.0-3.5 ppm. The signals of the carbon atoms in the other regions remain unchanged.

Characteristic changes also take place in the spectrum of the thioketal (XV). The singlet signal in the spectrum of (XV) at 62.70 ppm characterizes the common atom, C_3 of the 1,5-dithiaspiro[5.5]undecane rings F and A. The signals of the other three atoms of ring F are shown in an increase in the intensities of the signals at 25.69 ppm (C_2, C_{32}, and C_{34}) and 26.47 ppm (C_{16} and C_{33}).

The screening influence of the additional propanedithiol ring is experienced by the C_3 and C_5 carbon atoms, the signals of which are shifted about 6 ppm upfield as compared with the corresponding signals of methyl glycyrrhetate (II), while the signal of the C_{24} methyl group shifts downfield by 4.9 ppm. Table 3 gives the differences in the CSs of the carbon atoms of derivatives of the diastereomeric pair of 18α- and 18β-glycyrrhetic acids.

The most considerable differences in the spectra of the isomeric pairs of glycyrrhetic acid derivatives appear in the C_{28} and C_{16} signals. In the 18α- series (D/E-trans) the C_{28} signals are shifted upfield by from 11.2 to 12.4 ppm. The C_{16} signals are shifted downfield by 10.9-11.3 ppm. The signals of the C_{12} and C_{13} olefinic protons in the spectra of the derivatives of the 18α- series are also shifted downfield by 2.6-5.0 ppm.

As has been established [2], the C_{18} signal, which is sensitive to a change in the configuration of the glycyrrhetic acid molecule, appears 4.7-8.0 ppm upfield for the derivatives of the 18α- series as compared with the spectra of the compounds of the 18β-series.

The correlations detected unambiguously show the structures and configurations of the diastereoisomers.

A modification of the carboxy group in the 18α-glycyrrhetic acid series also finds its reflection in the spectra of these compounds.

Table 4 gives the increments of the CSs of the functional groups at C_{20} relative to the carboxy group of 18α-glycyrrhetic acid. The introduction into the 18α-glycyrrhetic acid molecule of the nitrogen-containing functions $NHCO_2CH_3$ (XXII) and NHCONHPh (XXI) leads to a downfield shift of the C_{29} signal by ~3 ppm, in contrast to the β-series (compounds II and VIII) in which the corresponding C_{29} signal shifts upfield by 0.2-0.3 ppm.

The values of the α increments of the functional groups mentioned in the 18β- series exceed those for the 18α- series (Δα - 8.5 ppm).

The signals of the β-carbons (C_{19}) undergo an upfield shift in compounds (XXII) and (XXI) of up to 1.5 ppm, while in the spectra of the analogous derivatives of the β-series (VII) and (VIII), these signals appear 2 ppm downfield as compared with the model compound (II).

EXPERIMENTAL

Type L silica gel (40/100 μ, Czechoslovakia) was used for chromatography, with the following solvent systems: 1) chloroform–ethanol (9:1) and 2) chloroform–ethanol (7:1). The spots were revealed with I_2 vapor. The substances were purified by crystallization and chromatography on columns of silica gel. The melting points were determined on a Boëtius microstage. Specific rotations were measured on a Perkin-Elmer 141 M polarimeter in a tube 1 dm long. IR spectra were recorded on UR-20 instrument in paraffin oil. ^1H NMR spectra were taken on a Tesla BS-497 instrument with a working frequency of 100 MHz in $CDCl_3$ with TMS as internal standard. ^{13}C NMR spectra were recorded on a JEOL-IX90Q spectrometer (22.50 MHz) in regimes with complete and off-resonance proton suppression. The samples were prepared in $CDCl_3$, CD_3OD, and DMFA-d_7, with TMS as internal standard. The widths of the field sweeps were 6024 and 2000 Hz and the resolution of the analog-digital converter was 0.74 and 0.24 Hz. The addition of the shift reagent $Eu(fod)_3$ was carried out in a "dry" box using previously dried solvents.

The derivatives of 18α- and 18β-glycyrrhetic acids (II-VI, IX, XI-XIV, and XVI-XVIII) were obtained by known methods [8-13], and the synthesis of the other compounds is described below.

3β-Propylenedithioketal of Methyl 3-Oxo-18βH-glycyrrhetate (XV). To 2 g (0.004 mole) of methyl 3-oxo-18βH-glycyrrhetate [9] was added 3.5 g (0.03 mole) of propanedithiol, and then the mixture was cooled to 0°C and 2.5 ml (0.02 mole) of boron trifluoride etherate was added slowly in drops. The solution was stirred at 0°C for 15 min, brought to room temperature, poured into 20 ml of 10% aqueous caustic soda solution, and extracted three times with 30-ml portions of chloroform. The chloroform solution was washed with water several times and was dried over $MgSO_4$. The solvent was evaporated off in vacuum and the residue was crystallized from methanol, to give 2.2 g (90%) of the desired product. mp 200-202°C; $[\alpha]_D^{20}$ +133° (*c* 0.0026 ; chloroform).

IR spectrum, ν, cm^{-1}: 1665 ($C^{11}=O$); 1735 ($COOCH_3$); 1420 ($S-CH_2$); 800–600 ($C-S$).

UV spectrum, $\lambda_{max}^{dioxane}$: 246 nm (log ε 4.058). Found, %: C 70.99; H 9.21; S 11.92; $C_{34}H_{53}O_3S_2$. Calculated, %: C 71.5; H 9.31; S 11.47. PMR spectrum, δ, ppm: 0.84 ($C^{28}H_3$); 1.07 ($C^{24}H_3$); 1.17 ($C^{23}H_3$); 1.18 ($C^{29}H_3$); 1.21 ($C^{27}H_3$); 1.29 ($C^{26}H_3$); 1.43 ($C^{25}H_3$); 3.72 ($O-CH_3$); 5.68 ($C^{12}-H$); 2.52 (C^9-H); 2.52–3.31 ($-S-CH_2-$).

Methyl 11-Oxo-3-deoxy-18βH-olean-12-en-30-oate (X). A mixture of 1 g of the dithioketal (XV) and 3 g of Raney nickel was boiled in 30 ml of absolute ethanol for 72 h. The catalyst was filtered off from the hot solution and, on cooling, the latter deposited the main reaction product (X). Yield 0.69 g (88%). mp 222-223°C; $[\alpha]_D^{20}$ –160.5° (*c* 0.004 ; chloroform). IR spectrum, ν, cm^{-1}: 1660 ($C^{11}=O$); 1735 ($COOCH_3$); UV spectrum, $\lambda_{max}^{dioxane}$: 246 nm (log ε 3.979). Found, %: C 79.39; H 10.08; $C_{31}H_{48}O_3$. Calculated, %: C 79.61, H 10.13. PMR spectrum, δ, ppm: 0.79 ($C^{23}H_3$); 0.82 ($C^{24}H_3$); 1.13 ($C^{25}H_3$); 1.35 ($C^{26}H_3$); 1.13 ($C^{27}H_3$); 0.86 ($C^{28}H_3$); 1.13 ($C^{29}H_3$);

TABLE 3. Differences of the CSs of the Carbon Atoms of Derivatives of 18α- and 18β-Glycyrrhetic Acids

Carbon	$\delta_{XVI}-\delta_{I}$	$\delta_{XVIII}-\delta_{II}$	$\delta_{XX}-\delta_{V}$	$\delta_{XIX}-\delta_{VI}$	$\delta_{XXII}-\delta_{VII}$	$\delta_{XXI}-\delta_{VIII}$
C_{12}	−4,47	−4,47	−4,63	−4,40	−4,37	−5,05
C_{13}	−2,58	−3,56	−3,27	−3,56	−3,30	−3,88
C_{14}	+0,13	−0 52	−0,52	−0,72	−0,75	−0,75
C_{15}	+0,82	+0,19	+0,14	+0,39	+0,33	+0,55
C_{16}	+11,27	+11,13	+10,93	+11,16	+11,04	+11,23
C_{17}	+4,10	+3,63	+3,43	+3,49	+3,65	+3,82
C_{18}	−7,60	−8 06	−7,31	−5,19	−4,86	−4,69
C_{19}	−4,62	−5,22	−5,68	−7,74	−7,39	−7,83
C_{20}	+0,53	−1,53	−1,44	+0 14	+1,29	+1,54
C_{21}	+1,65	+0,58	+0,36	+0,55	−0,62	+6 96
C_{22}	−9,16	−11,34	−8,36	−8,13	−6,83	−7,87
C_{28}	−12,30	−12,37	−12,44	−12,08	−12,01	−11,69

TABLE 4. Increments in the CSs of the Functional Groups at C_{20} Relative to the Carboxy Group of 18α-Glycyrrhetic Acid

Carbon	$\delta_{XVIII}-\delta_{XVI}$	$\delta_{XX}-\delta_{XVI}$	$\delta_{XIX}-\delta_{XVI}$	$\delta_{XXII}-\delta_{XVI}$	$\delta_{XXI}-\delta_{XVI}$
C_{13}	−1,34	−1,57	−1,60	−0,62	+0,20
C_{17}	−0,50	−0,19	−0,19	−0,03	+0,10
C_{18}	−0,26	0	+1,6	+1,37	+1,44
C_{19}	−0,37	−0,14	+0,81	−1,41	−0,59
C_{20}	−1,82	+10,55	+6,33	+11,28	+11,76
C_{21}	0,53	+0,33	+3,76	−0,35	−0,96
C_{22}	−0,15	+0,42	+0,26	+0,42	−0,26
C_{29}	−0,34	+0 20	−0,15	+3,17	+3,39

3.64 (OCH_3); 2.34 (C^9H); 5.60 (C^{12}—H).

3β-Acetoxy-11-oxo-18αH-olean-12-en-30-oyl Chloride (XX). A suspension of 1 g (0.002 mole) of 3-O-acetyl-18αH-glycyrrhetic acid (XVII) [9] in 50 ml of absolute ether was treated with 0.4 ml of dry pyridine, the mixture was cooled in an ice bath, and with vigorous stirring, 16 ml of thionyl chloride was added dropwise. The mixture was stirred for another 3 h, the precipitate was filtered off with suction without the access of air and it was washed on the filter with absolute ether. It was then dried in vacuum (1-2 mm Hg) at a temperature not exceeding 50°C. The yield of desired product was 0.94 g (92%). mp 285-286°C; $[\alpha]_D^{20}+91^\circ$ (*c* 0.004; chloroform). IR spectrum, ν, cm^{-1}: 1665 (C^{11}=O); 1735 (OAc); 1790 (COCl).

UV spectrum, $\lambda_{max}^{dioxane}$: 241 nm (log ε 4.029). Found, %: C 72.19; H 8.88; Cl 6.84. $C_{32}H_{47}O_4Cl$. Calculated, %: C 72.36; H 8.42; Cl 6.67. PMR spectrum: 0.88 (C^{23}—H_3, C^{24}—H_3); 1.14 (C^{25}—H_3); 1.35 (C^{26}—H_3) 1.27 (C^{27}—H_3); 0.73 (C^{28}—H_3); 1.22 (C^{29}—H_3), 2.06 ($OCOCH_3$); 4.60 (C^3—H); 2.29 (C^9—H); 5.63 (C^{12}—H).

3β-Acetoxy-11-oxo-18αH-norolean-12-en-20β-yl Isocyanate (XIX). I. With ice-bath cooling and stirring, a solution of 0.5 g (0.0076 mole) of sodium azide in 100 ml of water was added dropwise to a solution of 2 g (0.0038 mole) of the acid chloride (XX) in 100 ml of acetone. The reaction mixture was stirred at room temperature for 6 h. The excess of sodium azide was filtered off and the solvent was evaporated in vacuum at room temperature. This gave 1.6 g (90%) of 3-acetyl-18αH-glycyrrhetoyl azide. IR spectrum, ν, cm^{-1}: 1650 (C^{11}=O); 1740 (OAc); 2130 (CO—N_3).

II. A mixture of 1.62 g of the azide and 100 ml of dry toluene was boiled for 1 h, and then the solvent was distilled off in vacuum to dryness. The product was crystallized from absolute methanol, giving 1.5 g (96%) of the isocyanate (XIX). mp 252-253°C. IR spectrum, ν, cm^{-1}: 1660 (C^{11}=O); 1735 (OAc); 2265 (NCO). Found, %: C 75.23; H 9.18; N 2.68. $C_{32}H_{47}NO_4$. Calculated, %: C 75.40; H 9.29; N 2.75.

PMR spectrum, δ, ppm: 0.89 (C^{23}—H_3, C^{24}—H_3); 1.16 (C^{25}—H_3); 1.38 (C^{26}—H_3); 1.16 (C^{27}—H_3); 0.89 (C^{28}—H_3); 1.35 (C^{29}—H_3); 2.04 ($OCOCH_3$); 4.52 (C^3—H); 5.64 (C^{12}—H); 2.35 (C^9—H).

Methyl 3β-Acetoxy-11-oxo-18αH-norolean-12-en-20β-ylcarbamate (XXII). A solution of 0.5 g of the isocyanate (XIX) in 50 ml of absolute methanol was boiled for 20 h. The solvent was evaporated off in vacuum. Crystallization of the product from a mixture of chloroform and

hexane gave 0.5 g (94%) of the methyl carbamate (XXII). mp 293-294°C. $[\alpha]_D^{20}$ +88° (*c* 0.005; chloroform). IR spectrum, ν, cm^{-1}: 1650 (C^{11}=O); 1725 ($NHCO_2CH_3$); 1735 (OAc); 3385, 1520 (NH). UV spectrum, $\lambda_{max}^{dioxane}$: 244 nm (log ε 3.988). Found, %: C 73.10; H 9.39; N 2.29) $C_{33}H_{51}NO_5$. Calculated, %: C 73.16; H 9.49; N 2.59.

PMR spectrum, δ, ppm: 0.87 (C^{23}—H_3; C^{24}—H_3; C^{28}—H_3); 1.16 (C^{25}—H_3, C^{29}—H_3); 1.34 (C^{26}—H_3); 1.38 (C^{27}—H_3); 2.06 ($OCOCH_3$); 3.64 (OCH_3); 5.62 (C^{12}—H); 4.54 (C^5—H); 2.36 (C^9—H).

The corresponding methyl carbamate derivative (VII) of 18β-glycyrrhetic acid was obtained similarly with a yield of 94%. mp 289-290°C; according to the literature [11]: 290-291°C.

N-(3β-Acetoxy-11-oxo-18αH-norolean-12-en-20β-yl)-N'-phenylurea (XXI). A solution of 0.1 g (0.002 mole) of the 18αH-isocyanate (XIX) in 5 ml of dry chloroform was treated with 0.02 ml (0.002 mole) of freshly distilled aniline, and the mixture was boiled under reflux for 3 h.

Half the solvent was evaporated off and hexane was added until a precipitate of the 18αH phenylurea (XXI) appeared. The yield of desired product was 0.1 g (89%). mp 201-202°C; $[\alpha]_D^{20}$ +179° (*c* 0.0016 ; ethanol).

IR spectrum, ν, cm^{-1}: 1665-1640 (C^{11}=O, NHCONH); 1735 (OAc); 3450-3250, 1550-1530 (NH); 1600, 1500 (Ph); 755 (C—H arom.). UV spectrum, $\lambda_{max}^{C_2H_5OH}$: 203, 242, 286 nm (log ε 4.467, 4.469, 2.910). Found, %: C 75.57; H 8.99; N 4.28. $C_{38}H_{54}N_2O_4$. Calculated, %: C 75.71; H 9.03; N 4.64, R_f 0.72. [chloroform—ethanol (10:1)].

The 20-N-phenylurea derivative of methyl 18βH-acetoxyglycyrrhetate (VIII) was obtained similarly with a yield of 85%. mp, 196-197°C; $[\alpha]_D^{20}$ +204° (*c* 0.0044 , ethanol. UV spectrum, $\lambda_{max}^{C_2H_5OH}$: 205, 245, 285 nm (log ε 4.009, 4.074, 2.971). Found, %: C 75.31; H 8.99; N 4.40. $C_{38}H_{54}N_2O_4$. Calculated, %: C 75.71; H 9.03; N 4.64, R_f 0.76 [chloroform—ethanol (10:1)].

SUMMARY

1. The ^{13}C NMR spectra of a number of derivatives of 18α- and 18β-glycyrrhetic acids have been investigated and an assignment of the signals has been made. The influence of structural changes in the molecules of the compounds investigated on the chemical shifts of the carbon atoms has been traced.

2. The assignment of a number of signals has been confirmed with the use of the shift reagent $Eu(fod)_3$.

3. The C_{28} and C_{16} signals are the most sensitive to a change in the configuration at C_{18} in the spectra of glycyrrhetic acid derivatives.

4. A modification of the carboxy group of glycyrrhetic acid leads mainly to a change in the chemical shifts of the α-, β- and γ-carbon atoms of ring E.

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