HOMOGENEOUS HYDROGENATION AND DEUTERATION OF PENTACYCLIC TRITERPENOIDS: DOUBLE BONDS IN SIDE-CHAINS*

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The reduction of terminal double bonds in the side chains on the rings A and E of pentacyclic triterpenoids by means of tris(triphenylphosphine)rhodium chloride permits selective reduction of dienes and labelling with deuterium with a low scattering. The effect of the amount of the catalyst and the solvent used on the rate of reduction was studied in the case of 3β,28-diacetyl-betulin.

The exploitation of homogeneous catalysts for hydrogenations and deuterations of rigid sterically hindered systems has already been investigated, especially in the field of steroids. Stereospecificity, selectivity, and, under suitable conditions, a negligible scattering of deuterium (for example in[1]) was observed. However, pentacyclic triterpenoids have not been sufficiently studied from this point of view. As an example the hydrogenation of lupeol acetate may be mentioned[2]. In these investigations of the fragmentation mechanism by means of mass spectrometry the preparation of deuterated analogues of the substances under investigation with a minimum scattering of deuterium is often necessary. Therefore we considered it useful to study homogeneously catalyzed hydrogenation and deuteration of double bonds in various positions of the terpenic pentacyclic skeleton in the presence of tris(triphenylphosphine)rhodium chloride, the dependence of the reactions on the solvent used, on the amount of catalyst and the time of reaction.

First the hydrogenation of selected derivatives of 20(29)-lupene $(R = CH_3)$ or 30-nor-20(29)-lupene $(R = H)$ $I - X$ was investigated, *i.e.* the compounds of a disubstituted or monosubstituted double bond in the side chain, respectively. From Table I it is evident that the terminal double bond of lupene derivatives $I - X$ can be hydrogenated at room temperature and normal pressure without difficulty and that the reaction time depends to a considerable degree on the amount of catalyst. This dependence is represented in Table II for the case of hydrogenation of betulin di-

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acetate (III) in a mixture of benzene and ethanol $(4:1)$. On addition of further amounts of catalyst the reaction times may be achieved that are necessary for the hydrogenation of this double bond on a heterogeneous catalyst (for example hydrogenation of 100 mg of III on platinum under normal pressure is completed after about 1 h, ref.[10]). In the case of deuteration, however, the scattering of deuterium increases with increasing amount of the catalyst. In the case of 30-nor derivative X the favourable change of the steric environment of the double bond has a positive

TABLE I

Hydrogenation of lupene derivatives $I-X$ $RhCl(P(C_6H_5)_3)_3$, 20°C, 100 kPa, benzene–ethanol 4 : 1

Substrate	Amount		Time
	substrate mg	catalyst mg	min
I	100^e	100^b	240
II	150	100	360
III	100	50	480
IV	50	50	270
V	50	100	120
VI	80	40	510
VII	120	100	360
$VIII$	50	20	720
IX	40	40	270
X	30	30	180

[a] About 0·02 mmol; [b] about 0·1 mmol.

TABLE II

Dependence of the reaction time necessary for a quantitative hydrogenation of betulin diacetate (III) (100 mg) on the amount of $RhCl(P(C_6H_5)_3)_3$, 20°C, 100 kPa, benzene–ethanol 4 : 1 (10 ml)

| Substrate/catalyst (w/w)	1	2	3·3	5	10	20
Time	4	9	19	$>24^a$	$>24^b$	$>24^c$

[a] After 24 h 10% of III remained unreacted; [b] after 24 h 55% of III remained unreacted; [c] after 24 h 90% of III remained unreacted.

effect on the increase of the hydrogenation rate. The rate of hydrogenation can also be affected by a suitable choice of solvent. Polar solvents, or an addition of such solvents, enhance the reaction. However, poor solubility of some compounds of our series in polar solvents is a disadvantage. In Table III the effect of the solvents or their mixtures on the rate of hydrogenation of betulin diacetate (III) is compared. In deuterations the solvent used has an effect on the scattering of deuterium.

Further the hydrogenation of the isopropenyl double bond in A-seco derivatives XI, XII (ref.[3]) and $XIII$ (ref.[4]) was also investigated. A double bond in the position 4 has practically the same reactivity with respect to hydrogenation as the double bond in the position 29. In all three derivatives, $XI - XIII$, when a mixture of benzene–ethanol 4 : 1 was used as solvent and the amount of the catalyst equalled to that of its substrate, a quantitative conversion to dihydro derivative was achieved
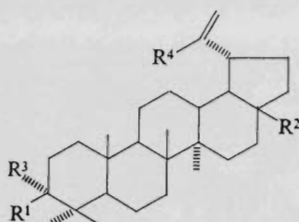
I, R^1 = OH, R^2 = =CH$_2$OH, R^3 = H, R^4 = CH$_3$
II, R^1 = OH, R^2 = CH$_2$OAc, R^3 = H, R^4 = CH$_3$
III, R^1 = OAc, R^2 = CH$_2$OAc, R^3 = H, R^4 = CH$_3$
IV, R^1 = OAc, R^2 = =CH$_2$OH, R^3 = H, R^4 = CH$_3$
V, R^1 = OAc, R^2 = COOH, R^3 = H, R^4 = CH$_3$
VI, R^1 = R^3 = H, R^2 = CH$_2$OH, R^4 = CH$_3$
VII, R^1 = OAc, R^2 = COOCH$_3$, R^3 = H, R^4 = CH$_3$
$VIII$, R^1 + R^3 = O, R^2 = COOCH$_3$, R^4 = CH$_3$
IX, R^1 = R^3 = H, R^2 = R^4 = CH$_3$
X, R^1 = OAc, R^2 = CH$_2$OAc, R^3 = R^4 = H
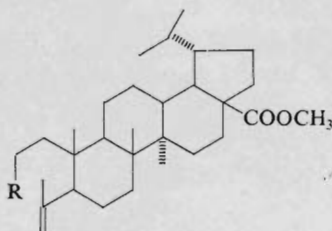
XI, R = COOCH$_3$
XII, R = CN
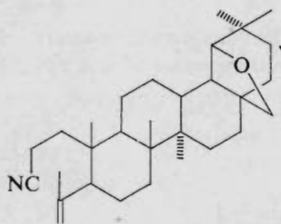
$XIII$

TABLE III
Dependence of the time of hydrogenation of betulin diacetate (*III*) (50 mg) on the medium. RhCl(P(C$_2$H$_5$)$_3$)$_3$ (50 mg), 20°C, 100 kPa

Solvent	Acetone	Benzene–methanol 4 : 1	Benzene–ethanol 1 : 1	Benzene–ethanol 4 : 1	Benzene–acetone 4 : 1	Benzene
Time, h	1·5	2·5	3	4	10	>12[a]

[a] After 12 h 30% of *III* remained unreacted.

TABLE IV
Melting points of hydrogenated and deuterated derivatives and the distribution of deuterium

Compound	M.p., °C			Distribution of deuterium, %				
	hydrogenated	hydrogenated (literature)	deuterated	d_0	d_1	d_2	d_3	d_4
I	276–279	270–280[9]	280	4	12	81	2	1
II	245–247	251–251[10]	246–249	3	13	82	1	1
III	258	259·5–260[9]	258–260	6	14	75	3	1
IV	249–253	258–259[9]	253–256	4	18	72	4	2
V	312–314	311–312·5[9]	305–308	2	15	81	2	0
VI	171–173	177–177·5[6]	173–175	5	15	75	4	1
VII	236–238	238·5–239[10]	234–237	2	10	78	7	3
VIII	189–192	194[9]	191–192	3	11	85	0	1
IX	181–183	188[9]	186–188	2	13	85	0	0
X	212–214	215–217[11]	211–214	3	20	73	4	1
XI	132–135	135–136[3]	131–133	2	13	79	4	2
XII	172–175	—	173	2	14	81	3	0
XIII	191–194	196–200[4]	192–194	2	22	76	1	0
XIV	208–210	210–214[5]	211–214	8	20	70	1	1
XV	178–180	181·5–182·5[6]	177–181	12	19	63	0	6
XVI	201–204	207·5[6]	205	7	14	77	1	1
XVII	231–233	233·5–234·5[7]	231	2	10	73	8	7
XVIII	181–183	—	182–185	2	12	71	10	5
XIX	132–134	135–137[3]	131–134	12	2	10	22	52[a]

[a] $d_5 = 1$, $d_6 = 1$.

after 3 h of hydrogenation. In the case of nitriles XII and $XIII$ the CN group was not attacked even when acetone was used as solvent and the reaction time was prolonged to 48 h.

Dienes − both with isolated, $XV-XVII$ (ref.[7]), and conjugated double bonds, XIV (ref.[5]) and $XVIII$ (this derivative was prepared from α-lupene on reaction with mercuric acetate[8]), − as well as the A-seco derivative XIX (ref.[4]) with two terminal double bonds, were hydrogenated in an analogous manner. In the case of compounds $XV-XVII$ dihydro derivatives with a saturated side chain (benzene–ethanol 4 : 1) were obtained, but the trisubstituted double bond in the position 16 or 17 (22) was attacked only negligibly under these conditions. In conjugated dienes XIV and $XVIII$

TABLE V

Deuteration of betulin diacetate (III) (50 mg) at various concentrations of $(RhCl(P(C_6H_5)_3)_3$; 20°C, 100 kPa, benzene–ethanol 4 : 1 24 h)

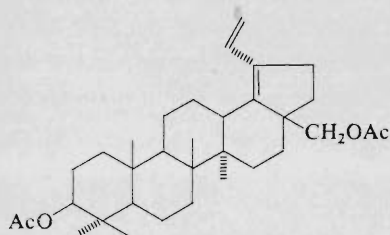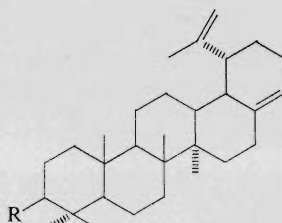| Catalyst mg	Conversion %	Distribution of deuterium
100	100	d_0 6%, d_1 14%, d_2 75%, d_3 3%, d_4 2%
50	100	d_0 6%, d_1 12%, d_2 77%, d_3 3%, d_2 2%
30	100	d_0 5%, d_1 10% d_2 80%, d_3 4%, d_4 1%
20	90	d_0 16%, d_1 20%, d_2 66%, d_3 2%, d_4 0%
10	50	d_0 15%, d_1 19%, d_2 61%, d_3 3%, d_4 2%
5	10	d_0 10%, d_1 27%, d_2 42%, d_3 11%, d_4 10%

TABLE VI

Deuteration of betulin diacetate (III) (50 mg) in various solvents $(RhCl(P(C_6H_5)_3)_3$ (50 mg), 20°C, 100 kPa, 6 h)

Solvent	Conversion, %	Distribution of deuterium
Acetone	100	d_0 2%, d_1 10%, d_2 82%, d_3 3%, d_4 4%
Benzene	50	d_0 7%, d_1 8%, d_2 80%, d_3 3%, d_4 1%
Benzene–ethanol 1 : 1	100	d_0 3%, d_1 12%, d_2 83%, d_3 2%, d_4 1%
Benzene–ethanol 4 : 1	100	d_0 6%, d_1 14%, d_2 75%, d_3 3%, d_4 2%
Benzene–acetone 4 : 1	75	d_0 8%, d_1 20%, d_2 70%, d_3 1%, d_4 1%
Benzene–methanol 4 : 1	100	d_0 2%, d_1 16%, d_2 62%, d_3 4%, d_4 16%

only a 10% conversion to dihydro derivative was achieved after 5 h of hydrogenation. For a quantitative hydrogenation of the terminal double bond acetone had to be used as solvent and the reaction time prolonged to 22 h. The tetrasubstituted double bond in the position 18 was not attacked even under these conditions. Hence, a selective hydrogenation of the mono- and disubstituted terminal double bond may be achieved. In the case of derivative *XIX*, however, the reactivity of both terminal double bonds could not be distinguished under any conditions. A tetrahydro derivative was always obtained. The melting points of the derivatives obtained on hydrogenation of compounds *I — XIX* are given in Table IV.

CH₂OAc → CH_2OAc

AcO

XIV

R

XV, R = H
XVI, R = OAc

AcO

XVII

XVIII

COOCH₃ → $COOCH_3$

CH₃OOC → CH_3OOC
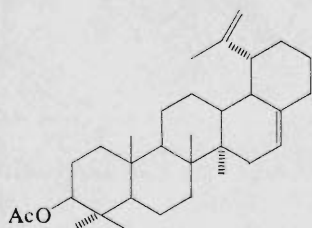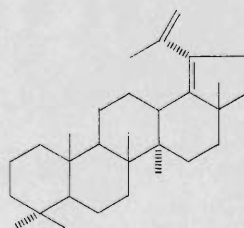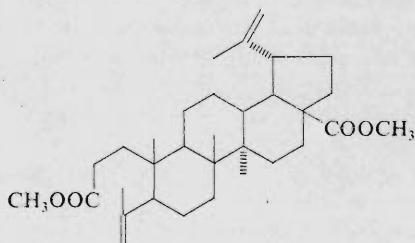
XIX

The series of compounds *I — XIX* was also deuterated under analogous conditions. The melting points and the distribution of the deuterium in the compounds obtained

are given in Table IV. The reaction times are analogous as in hydrogenations. The scattering of deuterium in the molecule increases mildly with increasing concentration of the catalyst. However, at extremely low concentrations of the catalyst the scattering of deuterium is also increased, as shown in Table V where the scattering of deuterium in the deuteration of betulin diacetate (III) is shown in dependence on the amount of the catalyst used. The scattering of deuterium is affected by solvents. Deuteration in benzene, acetone or mixtures of benzene and ethanol $(1 : 1 - 4 : 1)$ is accompanied by a weak scattering of deuterium. On the other hand, in a mixture of benzene and acetone, or especially in benzene–methanol, the scattering is considerable. Numerical values of the distribution in dependence on the solvent used are given in Table VI. During deuteration no exchange with benzene and acetone as solvents was observed. After 48 h of deuteration in benzene or acetone deuterium could not be detected in the solvent even when high-resolution mass spectrometry was applied.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. The distribution of deuterium in the molecule was determined by mass spectrometry on a Varian MAT 311 instrument, energy of the ionizing electrons 70 eV, ionizing current 1 mA, ion source temperature 200°C, temperature of direct inlet system 80—200°C. Tis(triphenylphosphine)rhodium chloride was prepared according to ref.[12]. The solvents for reductions were dried in the conventional manner and distilled. Deuterium was obtained by electrolysis of heavy water (99·9% ^2H_2O).

General Procedure for Hydrogenation and Deuteration

The unsaturated compound (100 mg) was dissolved in the corresponding solvent (10 ml) in a 50 ml flask and $RhCl(P(C_6H_5)_3)_3$ (100 mg) was added to the solution. The flask was connected with a hydrogenation apparatus, evacuated and rinsed twice with hydrogen (deuterium). After final filling with hydrogen (deuterium) the content was stirred with a magnetic stirrer. The degree of conversion was determined both on the basis of the consumption of the gas and by subtracting samples for thin-layer chromatography and mass spectrometry. Thin-layer chromatography was carrried out on silica gel impregnated with 10% of silver nitrate using detection with sulfuric acid spray (10%) and heating. When the reaction was over the mixture was evaporated in a vacuum and extracted with boiling n-hexane (30 ml). The hexane solution was filtered through a small column of alumina (activity II according to Brockmann) and the filtrate was evaporated and crystallized.

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