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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Re: Expediente No. 07-076.578
Solicitud de patente de invención titulada: "18-METIL-19-NOR-17-PREGN-4-
EN-21,17-CARBOLACTONAS, ASÍ COMO PREPARACIONES
FARMACÉUTICAS QUE LAS CONTIENEN".
Solicitante: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT
Nuestra Ref.: P2007/000115

**RESPUESTA AL OFICIO (sin número asignado), NOTIFICADO POR FIJACIÓN EN
LISTA No. 207, DE FECHA 03 DE JUNIO DE 2011.
(REQUERIMIENTO ARTÍCULO 46)**

Yo, CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, reasumiendo el poder a mi conferido por la sociedad Bayer Schering Pharma Aktiengesellschaft, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa del siguiente documento solicitado por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

1) NICKISCH K ET AL: "ALDOSTERONE ANTAGONISTS. 4. SYNTHESIS AND ACTIVITIES OF STEROIDAL 6,6-ETHYLENE-15,16-METHYLENE 17-SPIROLACTONES". JOURNAL OF MEDICINAL CHEMISTRY. 19910101 AMERICAN CHEMICAL SOCIETY. WASHINGTON, US. – ISSN 0022-2623; VOL: 34. PAGES 2464 – 2468.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Copia simple Poder
Artículo mencionado

Aldosterone Antagonists. 4. Synthesis and Activities of Steroidal

6,6-Ethylene-15,16-methylene 17-Spirolactones

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Several steroidal 6,6-ethylene-15,16-methylene 17-spirolactones were synthesized to find new progestogens that exhibit both progestational and antimineralocorticoid activities. The influence of substituents in the 10- and 13-position of the steroidal framework on both properties was investigated. It was found that only compound 12, carrying methyl groups at the 10- and 13-positions, possesses high progestational and antimineralocorticoid activity.

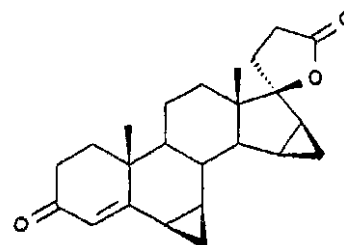
The development of steroidal aldosterone antagonists as potassium-retaining diuretics was initiated by the observation that progesterone acts as a competitive antagonist of the renal action of mineralocorticoid hormones.^{1,2} Extensive molecular modifications led to the synthesis of the antimineralocorticoid spironolactone, a compound that still exhibits weak progestational activity.³⁻⁵ Our research efforts during the past years have been primarily concerned with the development of new potent antialdosterone derivatives and have been culminated in the synthesis of 6 β ,7 β :15 β ,16 β -dimethylene spiro lactones 1 and 2.^{6,7}

Both compounds, when tested in rats, exhibited a 7- to 8-fold higher aldosterone antagonistic potency compared to that of spironolactone.^{8,9} Compound 1 could not be developed as a diuretic because of its progestational activity as measured in the endometrium transformation test and pregnancy maintenance test.^{10,11} Especially in rats 1 showed a progestational potency comparable to cyproterone acetate.¹⁰ These data suggested that aldosterone antagonistic and progestational activity are observed in the same dose range for these compounds.

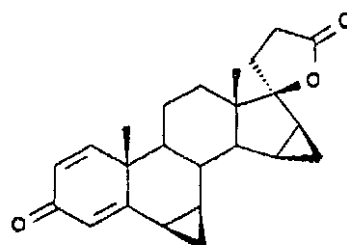
This combination of activities is only found in naturally occurring progesterone, whereas the synthetic derivatives of 17-hydroxyprogesterone and 19-nortestosterone are only potent progestational agents but do not exhibit antimineralocorticoid activity.⁸ The potential advantages of a new progestogen with a profile compared to progesterone have been emphasized^{8,11} especially with respect to the development of a new type of progestogen-estrogen combination for fertility control. Upon taking oral contraceptives, some women exhibit an increasing in blood pressure.¹² Hypertension is generally a contraindication for taking the birth control pill. With a progestogen exhibiting antimineralocorticoid activity, the increase in blood pressure

should be counteracted, therefore allowing predisposed women to choose a hormonal contraceptive as fertility control method for the first time.

The optimal ratio between aldosterone antagonistic and progestational activity has to be carefully evaluated. Probably the most obvious question is how much antimineralocorticoid activity is necessary at fully active progestational doses. To answer this question, we were looking for derivatives of compound 1 exhibiting comparable aldosterone antagonistic potency but higher progestational potency compared to 1.



1



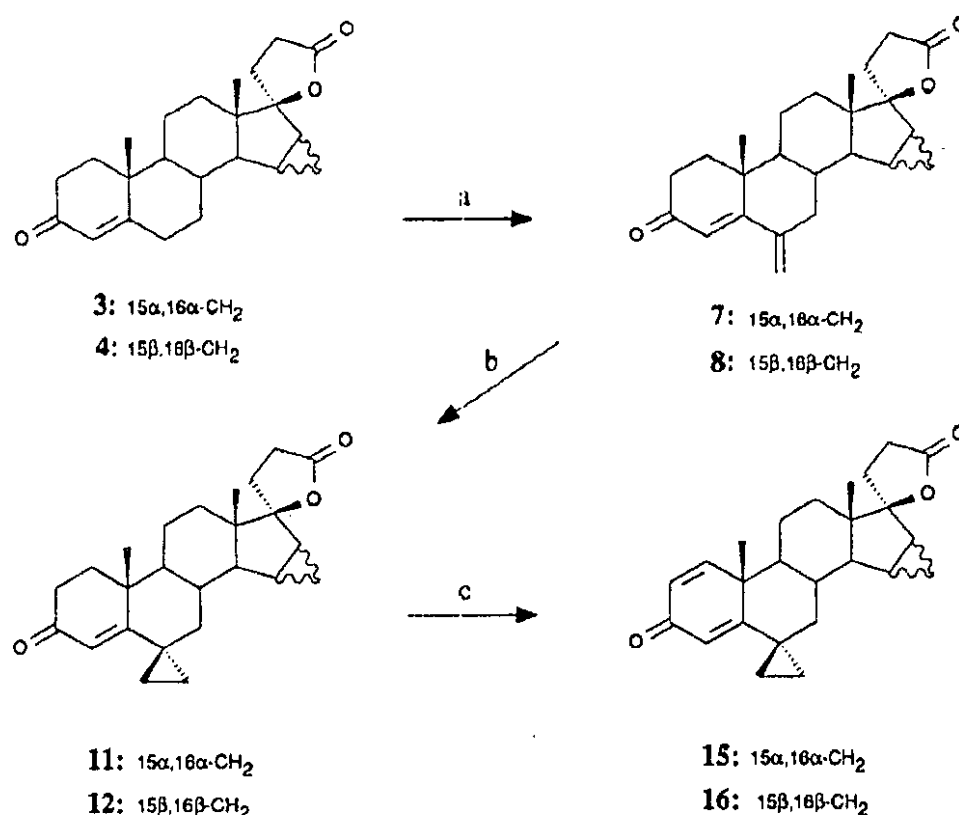
2

Chemistry

The structure-activity relationship of spirorenone analogues has been reported.¹³ Molecular modification of 1 produced only compounds with reduced aldosterone antagonistic potency and reduced binding to the progesterone receptor. We therefore investigated other basic structures showing both activities. For progestational activity the importance of substituents in the 6-position has been emphasized.¹⁴ Optimal activity is found with rather small and moderate lipophilic substituents, such as methyl or chlorine, but aldosterone antagonists with these substitu-

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Scheme 1^a

^a (a) 1. pyrrolidine, MeOH, reflux; 2. CH₂O, EtOH, benzene; 3. HCl, dioxane; (b) (CH₃)₃S(O)I, NaH, DMSO; (c) DDQ, toluene, 100 °C.

ents are lacking oral bioavailability. Both requirements are fulfilled by a 6,6-ethylene moiety. Moreover it has been reported that spiro-lactone derivatives with this moiety exhibit aldosterone antagonistic activity.¹⁵ The progestational activity depends on the nature of substituents at the 17 α -position and to some extent at the 10- and 13-positions of the steroid nucleus.¹⁶ Generally speaking 19-nor derivatives are more potent than 10-methyl compounds. The highest progestational potency is found when the 10-position is substituted by a hydrogen and the 13-position with an ethyl group (e.g., norgestrel).¹⁶ Only a few examples about the systematic comparison of the different series of steroid frameworks on the aldosterone antagonistic activity have been reported.¹⁷ For this reason, we decided to investigate the influence of the substitution pattern in the 10- and 13-position of the steroid framework on the progestational and antimineralocorticoid activity of 6,6-ethylene-15,16-methylene 17-spirolactones.

As starting material for our efforts we chose the 15,16-methylene spiro-lactones 3–6. The synthesis of 3 and 4 has been reported.¹⁸ Compounds 5 and 6 were prepared under analogous conditions.¹⁹ The transformation of the 13-methyl derivatives 3 and 4 to the 6,6-ethylene compounds 11 and 12 was accomplished in a four-step sequence (Scheme I). Reaction of the unsaturated ketones with pyrrolidine generated enamines, which were reacted with

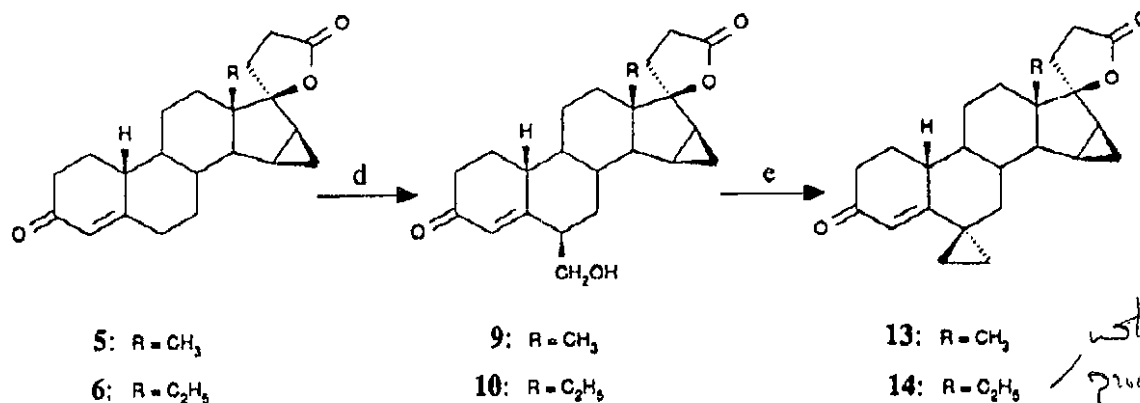
aqueous formaldehyde to form the hydroxymethyl derivatives. The crude material was transformed to the 6-methylene compounds 7 and 8. The dienes were converted to the 6,6-ethylene derivatives 11 and 12 by reaction with trimethylsulfoxonium iodide and sodium hydride.

For the synthesis of the 19-nor derivatives 13 and 14, a slightly different method of synthesis was applied. The starting materials 5 and 6 were transformed via the enamines to the 6-hydroxymethyl derivatives 9 and 10. The stereochemistry of the 6-substituent was investigated by NMR. The H-4 shows only one allylic coupling of 2 Hz to the H-10, proving that the hydroxymethyl group is in the β -position. All attempts to transform the hydroxymethyl steroids 9 or 10 to the corresponding dienones either under acidic or after transformation to the tosylates under basic conditions were unsuccessful. Only dimeric steroids could be isolated, but their accurate structures were not determined. The desired 6,6-ethylene compounds were finally synthesized by transformation of the hydroxymethyl derivatives 9 and 10 to the tosylates, which were reacted with an excess of trimethylsulfoxonium iodide and sodium hydride in an elimination addition process (Scheme II). The 1,2 double bond was introduced in compounds 11 and 12 by dehydrogenation with DDQ to yield 15 and 16.

Biological Results and Discussion

The most potent antimineralocorticoid compound of this series is clearly the 15 β ,16 β -methylene derivative 12, exhibiting a 5-fold higher potency compared to the standard drug spironolactone (oral administration to adrenalectomized rats infused with aldosterone, Table I). The introduction of a 1,2 double bond to yield 16 diminished the aldosterone antagonistic potency. The 19-nor compound 13 and the 13-ethyl-19-nor derivative 14 both showed reduced antimineralocorticoid activity when compared with 12. The 15 α ,16 α -methylene analogue 11 also

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Scheme II^a

^a(d) 1. pyrrolidine, MeOH, reflux; 2. CH₂O, EtOH, benzene; (e) 1. *p*-TosCl, pyridine; 2. (CH₃)₃S(O)I, NaH, DMSO.

not tested for
pregn. st. active.
(not soluble enough)

Table I. Biological Activities of Spirolactones

compd	antialdosterone activity maximal relative potency ^a (spironolactone = 100; 95% confidence limits)	progesterone receptor competition factor ^c (progesterone = 1)
11	<100 ^b	2.1
12	507 (393-598)	1.1
13	≈100 ^b	0.5
14	<100 ^b	
15	≈100 ^b	4.0
16	≈100 ^b	2.3
1	685 (549-1095)	2.7

^aRelative potency calculated for the hour of maximal activity after oral administration. ^b<, ≈: lower, not significantly different relative potency estimated from single-dose experiments in which the test compound was administered at a 2-fold higher dose (53.6 mg/kg) than the standard spironolactone (26.8 mg/kg). ^cThe competition factor is defined as the ratio of concentration of the test compound to progesterone causing the same specific displacement of the radiolabeled standard from the receptor (measured at 50% displacement).

exhibited decreased antimineralocorticoid activity compared to that of compound 12.

All compounds bind very strongly to the progesterone receptor exhibiting comparable (12) or even higher affinity (13) to the receptor than the naturally occurring progesterone. As it is found with 17 α -ethynyl compounds, the 15 β ,16 β -methylene-19-nor derivative 13 exhibited a stronger binding to the progesterone receptor than the 15 β ,16 β -methylene-10-methyl derivative 12.¹⁶ Unfortunately, the 13-ethyl-19-nor derivative 14 could not be tested *in vitro* because of lack of solubility.

The basic tests clearly showed that only compound 12 exhibits the desired combination of high antimineralocorticoid potency and strong binding to the progesterone receptor. Therefore the progestational activity of the 6,6-ethylene derivative 12 was evaluated in comparison to the 6 β ,7 β -methylene derivative 1 *in vivo* by using two relevant animal models¹⁰ (endometrium transformation test in estrogen-primed juvenile rabbits and pregnancy maintenance tests in rats, Table II). When tested subcutaneously in rabbits, compound 12 exhibited a progestational activity at least 3-fold higher than that of compound 1, whereas after oral treatment no difference in activity was observed. In the pregnancy maintenance test in rats (*sc* injection), the progestational activity of the 6,6-ethylene derivative 12 was about 10-fold higher compared to that of compound 1. There is a reasonable correlation between the results of the pregnancy maintenance test and progestational activity in man.¹⁰ Ongoing clinical trials are intended with compound 1 to show if the combination of aldosterone antagonistic with progestational

Table II. Progestational Activity: Endometrium Transformation Test in Rabbits after Subcutaneous and Oral Administration and Pregnancy Maintenance Test in Rats after Subcutaneous Treatment

compd	dose, mg	endometrium transformation test McPhail index		pregnancy maintenance test % inhibition
		sc	po	
12	3.0			38
	1.0		2.1	63
	0.3	2.9	1.6	63
	0.1	2.6	1.6	58
	0.03	1.3	1.5	82
1	0.01			12
	10.0			0
	3.0		2.4	52
	1.0	2.7	2.4	85
	0.3	2.4	1.9	74
	0.1	1.2	1.6	3
				0

activity is sufficient to overcome typical progesterone side effects. During the course of these studies it will also become evident whether a substance such as 12, which exhibits reduced antimineralocorticoid activity, would be more suitable for this purpose.

Methods

Antialdosterone Activity in Rats.^{20,21} Adrenalectomized male rats (Wistar strain) with a body weight of 140-160 g were treated with glucocorticoids (1 mg of flucortolone caproate/kg *sc* on the day of surgery and 10 mg of flucortolone/kg *sc* 1 day before the diuresis experiment, which was performed 5 days after adrenalectomy). These glucocorticoid-substituted rats were infused intravenously with a saline-glucose solution (0.05% NaCl, 5% glucose) containing aldosterone (50 μ g/L) at a rate of 3 mL/h for 15 h. The aldosterone antagonist was administered 1 h before the start of the aldosterone infusion. Urine excretion was measured in fractions of 1 h. Sodium and potassium concentrations in urine were determined by flame photometry. The antialdosterone activity was assessed by the ability of the compounds to reverse the aldosterone effect on the urinary Na/K ratio. The various antialdosterone derivatives and spironolactone were administered at three oral doses of 6.7, 13.4, and 26.8 mg/kg. The dose-response relationship was tested for each fraction

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Table III. 6,6-Ethylene Carbolactones

compd	prep method	yield, %	mp, °C	formula	Anal.	¹ H NMR (100 MHz, CDCl ₃), δ		
						18-CH ₃	19-CH ₃	other
11	A	21	177	C ₂₅ H ₃₂ O ₃	C, H, O	1.20	1.24	5.61 (s, 1, H-4)
12	A	17	184	C ₂₅ H ₃₂ O ₃	C, H, O	1.01	1.22	5.61 (s, 1, H-4)
13	B	21	214	C ₂₄ H ₃₀ O ₃	C, H, O	1.08		5.7 (d, <i>J</i> = 1.5 Hz, 1, H-4)
14	B	17	165	C ₂₅ H ₃₂ O ₃	C, H, O	0.85 (t)		5.7 (s, 1, H-4)
15	C	87		C ₂₅ H ₃₀ O ₃	C, H, O	1.25	1.35	5.98 (d, <i>J</i> = 2 Hz, 1, H-4) 6.17 (dd, <i>J</i> = 10 + 2 Hz, 1, H-2) 7.0 (d, <i>J</i> = 10 Hz, 1, H-1)
16	C	67	200	C ₂₅ H ₃₀ O ₃	C, H, O	1.07	1.33	5.98 (d, <i>J</i> = 2 Hz, 1, H-4) 6.17 (dd, <i>J</i> = 10 + 2 Hz, 1, H-2) 6.97 (d, <i>J</i> = 10 Hz, 1, H-1)

by regression analysis after logarithmic transformation of the doses. The potency of the standard substance, spiro-nolactone, was allocated the value of 100.

Binding to Progesterone Receptor.²² For the determination of the affinity of the test substance to the progesterone receptor isolated from the rabbit uterus, tritiated progesterone was used as ligand, and the competition factors are defined as the multiple of the concentration to obtain displacement equivalent to the standard. A high competition factor indicates low binding strength, and a low competition factor indicates high affinity.

Endometrium Transformation Test.¹⁰ Castrated, infantile female rabbits (albino New Zealand) weighing 800–1000 g were administered a daily subcutaneous dose of 0.5 µg of estradiol for 6 days (priming). Thereafter, the animals were treated with varying doses of test compounds (po and sc) for 5 days. On day 12, the animals were sacrificed, and the uteri were excised for histological studies. The rate of the glandular development in endometrium was evaluated by using the McPhail scale (1–4; 1 = inactive, 4 = maximal development of the glands).

Pregnancy Maintenance Test.¹⁰ Pregnant rats were ovariectomized on day of pregnancy. This treatment leads to interruption of pregnancy. The ability of compounds to prevent the loss of pregnancy was used as parameter of gestagenic activity. Daily treatment was performed from day 8 to 21 of pregnancy. At autopsy day 22 the rate of pregnant animals and the rate of surviving fetuses was assessed (10 fetuses/dose = 100 % maintenance). In order to obtain an optimal uterine response to gestagens a dose of 1 µg estrone/day was injected sc in combination with the tested dose of a compound.

Experimental Section

All melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. NMR spectra were taken in CDCl₃ on a Bruker MX 90 or a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard unless otherwise stated. Ultraviolet spectra were obtained in methanol on a Cary 14 UV spectrophotometer. Infrared spectra were obtained in KBr tablets on Perkin-Elmer Model 621 and 580 B infrared spectrophotometer. Optical rotations are specific rotations taken in CHCl₃ (0.5 %).

Method A. 6:15β,16β-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (8). A solution of 4.1 g (0.0116 mol) of 4 in 31 mL of methanol was heated under reflux with 2.05 mL of pyrrolidine for 15 min. After cooling in an ice bath, the thus-formed precipitate was suctioned off, washed with a small amount of methanol, and dried. This material was dissolved in 90 mL of ethanol, and 45 mL of benzene and 4.5 mL of a 37% strength formalin solution was added dropwise. After a reaction period of 30 min, the reaction solution was evaporated to dryness under vacuum. The residue was chromatographed on silica gel

with hexane/ethyl acetate and the oily residue was agitated for 2 h in 77 mL of dioxane with 9.1 mL of half-concentrated hydrochloric acid. The reaction solution was then combined with an excess of sodium bicarbonate and filtered off from the inorganic salts. The filtrate was diluted with ether and washed with water. After drying and evaporation, the residue was chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yielded 1.2 g (28%) of 8: mp 173 °C; UV ϵ_{261} = 11300; IR 1770, 1670, 1620, 1590 cm⁻¹; NMR 1.0 (s, 3, C-18), 1.15 (s, 3, C-19), 5.04 (s (br), 1) and 5.12 (s (br), 1) =CH₂, 5.92 (s, 1, 4-H) ppm. Anal. (C₂₄H₃₀O₃) C, H, O.

6:15α,16α-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (7). Under the above-described conditions, 5.9 g (0.0166 mol) of 3 was transformed to 2.26 g (37%) of 7: mp 164 °C; UV ϵ_{262} = 11300; IR 1765, 1675, 1635, 1600 cm⁻¹; NMR 1.15 (s, 3, C-18), 1.23 (s, 3, C-19), 5.02 (s (br), 1) and 5.13 (s (br), 1) =CH₂, 5.94 (s, 1, 4-H) ppm. Anal. (C₂₄H₃₀O₃) C, H, O.

6,6-Ethylene-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (12). At room temperature, 1.41 g (0.0064 mol) of trimethylsulfoxonium iodide was agitated for 1.5 h with 239 mg (0.0055 mol) of sodium hydride (55% oil suspension) in 21.5 mL of DMSO. Under argon, 1.14 g (0.0031 mol) of 8 was added to the solution and was stirred for 50 min at room temperature. The reaction mixture was then poured into ice water and was weakly acidified with 2 N sulfuric acid. The thus-formed precipitate was filtered off and taken up in methylene chloride. After drying and evaporation, the residue was chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yielded 726 mg (61%) of 12: mp 184 °C; UV ϵ_{248} = 14200.

6,6-Ethylene-15α,16α-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (11). Under the described conditions 1.87 g (0.0051 mol) of 7 was transformed to 1.1 g (57%) of 11: mp 177 °C; UV ϵ_{247} = 13900.

Method B. 6β-(Hydroxymethyl)-15β,16β-methylene-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (9). A solution of 4.0 g (0.0117 mol) of 5 in 35 mL of methanol was combined with 2 mL of pyrrolidine and heated for 20 min under reflux. After cooling, the thus-formed precipitate was suctioned off and washed with a small amount of cold methanol and dried. This material was dissolved in 43.6 mL of benzene and 87.2 mL of ethanol, and 4.3 mL of a 37% strength formalin solution was added dropwise. The mixture was stirred for 1 h at room temperature and concentrated under vacuum. The resultant crude mixture was chromatographed on silica gel, thus obtaining after recrystallization from diisopropyl ether 1.9 g (44%) of 9: mp 247 °C; IR 3410, 1765, 1670, 1650, 1615 cm⁻¹; NMR 1.07 (s, 3, C-18), 3.76 (m, 2, CH₂OH), 5.94 (s, 1, H-4) ppm. Anal. (C₂₃H₃₀O₄) C, H, O.

6β-(Hydroxymethyl)-18-methyl-15β,16β-methylene-19-nor-17α-pregn-4-ene-21,17-carbolactone (10). Under the above described conditions, 5.0 g (0.0141 mol) of 6 was transformed to 2.33 g (43%) of 10: IR 3450, 1770, 1670, 1610 cm⁻¹; NMR 0.86 (t, *J* = 7 Hz, 3, CH₂CH₃), 2.71 (dt, *J* = 5 + 7 Hz, 1, H-6), 3.76 (m, 2, CH₂OH), 5.95 (d, *J* = 2 Hz, 1, H-4) ppm. Anal. (C₂₄H₃₂O₄) C, H, O.

6,6-Ethylene-15β,16β-methylene-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (13). A solution of 2.06 g (0.0056 mol) of 9 in 20 mL of pyridine was combined with 3.14 g (0.0165 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred for 3 h at room temperature, combined with 0.2 mL of water, and agitated for another hour, and the reaction mixture was precipitated into ice water. The resultant precipitate was filtered off, washed with

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water, and dried. A solution of 3.84 g (0.0174 mol) of trimethylsulfonium iodide in 75 mL of DMSO was combined with 586 mg (0.013 mol) of sodium hydride (55% oil suspension) and agitated for 1 h at room temperature. To this solution was added the dried crude tosylation product dissolved in 2 mL of DMSO dropwise. The reaction mixture was stirred for 30 min and precipitated into ice water. The resultant crude product was chromatographed on silica gel, thus producing 985 mg (48%) of 13: mp 214 °C; UV $\epsilon_{247} = 13500$.

6,6-Ethylene-18-methyl-15 β ,16 β -methylene-3-oxo-19-nor-17 α -pregn-4-ene-21,17-carbolactone (14). Under the above described conditions 372 mg (0.001 mol) of 10 was transformed to 145 mg (39%) of 14: mp 165 °C; UV $\epsilon_{247} = 14700$.

Method C. 6,6-Ethylene-15 β ,16 β -methylene-3-oxo-17 α -pregna-1,4-diene-21,17-carbolactone (16). A solution of 670 mg (0.0018 mol) of 12 and 670 mg (0.003 mol) of DDQ in 13.6 mL

of toluene was stirred for 5 h at 100 °C. The reaction solution was then diluted with ether, washed with water sodium bicarbonate solution and water, dried, and evaporated. The residue was then chromatographed on silica gel. After recrystallization from diisopropyl ether/acetone, 445 mg (67%) of 16 was obtained: mp 200 °C; UV $\epsilon_{245} = 15200$.

6,6-Ethylene-15 α ,16 α -methylene-3-oxo-17 α -pregna-1,4-diene-21,17-carbolactone (15). Under the above-described conditions, 600 mg (0.0016 mol) of 11 was transformed to 520 mg (87%) of 15 as an oil: UV $\epsilon_{242} = 14600$.

Registry No. 3, 67372-62-7; 4, 67372-68-3; 5, 101765-54-2; 6, 101765-39-3; 7, 101834-16-6; 8, 84529-99-7; 9, 133753-23-8; 10, 133753-24-9; 11, 101834-17-7; 12, 101765-35-9; 13, 101765-58-6; 14, 133753-25-0; 15, 101834-18-8; 16, 101765-36-0; formalin, 50-00-0; aldosterone, 52-39-1.

Synthesis and Evaluation of Antiinflammatory Activities of a Series of Corticosteroid 17 α -Esters Containing a Functional Group

Hiroaki Ueno,* Akira Maruyama, Motoyoshi Miyake, Etsuko Nakao, Kenichiro Nakao, Kohei Umezu, and Issei Nitta

Pharmaceuticals Laboratory, Research Center, Mitsubishi Kasei Corporation, 1000 Kamoshida-cho, Midori-ku, Yokohama-city, Kanagawa 227, Japan. Received January 14, 1991

A series of 21-desoxy-21-chlorocorticosteroids that contain a functionalized ester group at 17 α has been prepared and examined to separate their systemic activity from topical antiinflammatory activity. Introduction of the functionalized ester group at 17 α was carried out by an acid-catalyzed formation of cyclic ortho esters with 17 α ,21-hydroxyl groups of corticosteroids and subsequent acid-catalyzed hydrolysis. As for the functional group, chloro, methoxy, acetoxy, cyano, cyclopropyl, or alkoxycarbonyl group was introduced at the terminal carbon atom of the 17 α -alkanoate group. The topical antiinflammatory activity and systemic activity of these compounds were examined and found to be significantly dependent on the functionalities in the 17 α -esters. Among these derivatives, a series of 17 α -(alkoxycarbonyl)alkanoates (17 α -OCO(CH₂)_nCOOR) showed an excellent separation of the systemic activity from topical activity. The effects of the number of methylene groups (*n*) and of the alkyl groups of the ester (R) on either topical or systemic activity of the corticosteroid derivatives were also investigated.

Introduction

Since hydrocortisone was introduced into dermatological use,¹ many structural modifications of the hydrocortisone molecule have been made with the aim at enhancing antiinflammatory potency. Important structural modifications include halogenation,² methylation,³ and introduction of a double bond at C-1 position of the steroidal skeletons.⁴

Also, it is confirmed that esterification of the 17 α -and/or 21-hydroxyl groups⁵ and replacement of the 21-hydroxyl group with a halogen atom⁶ enhance the topical antiinflammatory activity due to improved penetration of

the skin and to increased affinity for the glucocorticoid receptor.⁷

As a result of these modifications, 21-chloro-9 α -fluoro-11 β ,17 α -dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17 α -propionate (clobetasol propionate, CP) is found to have the strongest topical antiinflammatory activity in clinical use.⁸ On the other hand, CP also shows severe adverse effects such as thymolysis and dermal atrophy.⁹

In the field of glucocorticoids, little success has been achieved in completely separating undesired side effects from topical antiinflammatory activity except for 21-carboxylate⁹ and 17 β -carboxylate¹⁰ derivatives. However, the antiinflammatory activity of neither derivatives is as strong as that of CP. Teutsch et al.¹¹ and Kertesz and

- (1) Sulzberger, M. B.; Witten, V. H. *J. Invest. Derm.* 1952, 19, 101.
- (2) (a) Fried, J.; Sabo, E. F. Synthesis of 17 α -Hydroxycorticosterone and Its 9 α -Halo Derivatives From 11-Epi-17 α -hydroxycorticosterone. *J. Am. Chem. Soc.* 1953, 75, 2273. (b) Fried, J.; Sabo, E. F. 9 α -Fluoro Derivatives of Cortisone and Hydrocortisone. *Ibid.* 1954, 76, 1455.
- (3) (a) Spero, G. B.; Thompson, J. L.; Magerlein, B. J.; Hanze, A. R.; Murray, H. C.; Sebek, O. K.; Hogg, J. A. Adrenal Hormones and Related Compounds. 4. 6-Methyl Steroids. *J. Am. Chem. Soc.* 1958, 78, 6213. (b) Arth, G. E.; Fried, J.; Johnston, D. B. R.; Hoff, D. R.; Sarett, L. H.; Silber, R. H.; Stoerk, H. C.; Winter, C. A. 16-Methylated Steroids. 2. 16 α -Methyl Analogues of Cortisone, a New Group of Antiinflammatory Steroids. 9 α -Halo Derivatives. *Ibid.* 1958, 80, 3181. (c) Oliveto, E. P.; Rausser, R.; Herzog, H. L.; Herschberg, E. B.; Tolksdorf, S.; Eisler, M.; Perlman, P. L.; Pechet, M. M. 16-Alkylated Corticoids. 3. 16 β -Methyl-9 α -fluoroprednisolone 21-Acetate. *Ibid.* 1958, 80, 6687.
- (4) Herzog, H. L. *Science* 1955, 121, 178.
- (5) McKenzie, A. W.; Atkinson, R. M. *Arch. Derm.* 1964, 89, 741.
- (6) Phillips, G. H. *Mechanism of Topical Corticosteroid Activity*, Glaxo Symposium; Churchill Livingstone: London, 1976.

- (7) Solo, A. J.; Trampusch, K. M.; Szeto, D. W.; Suto, M. J. Relative Affinity of 17 α - and/or 21-Esters and 17 α ,21-Diesters of Cortisol for a Glucocorticoid Receptor from Thymocytes. *J. Med. Chem.* 1982, 25, 747.
- (8) Carruthers, J. A.; August, P. J.; Staughton, R. C. D. Observations on the Systemic Effect of Topical Clobetasol Propionate (Dermovate). *Br. Med. J.* 1975, 4, 203.
- (9) (a) Lee, H. J.; Soliman, M. R. I. Anti-Inflammatory Steroids Without Pituitary-adrenal Suppression. *Science* 1982, 215, 989. (b) Lee, H. J.; Trotter, R. Antiinflammatory Activity of Two Novel Derivatives of Prednisolone. *Res. Commun. Chem. Pathol. Pharmacol.* 1980, 27, 611. (c) Lee, H. J.; Bird, J.; Kim, H. P. Topical Anti-Inflammatory Activity of Esters of Steroid 21-Oic Acids. *Steroids* 1986, 47, 35.
- (10) Phillips, G. H.; Bain, B. M.; English, A. F.; Woollett, E. A. Chloromethyl 17 α -acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylate. German Patent 2,904,614, 1979; *Chem. Abstr.* 1979, 92, 6814q.



9-INT. 81962/584

[Signature]



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LEGALIZACION
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12/03/2007 13:51:54 \$39.00
12/03/2007 13:51:46 \$20.00

1 FOLIO 85.- PRIMERA COPIA.- ESCRITURA NÚMERO: VEINTICUATRO.-
2 SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Dagmar a favor de
3 OLARTE, Carlos Reinaldo y otro del Poder otorgado por BAYER SCHERING
4 PHARMA AG.- En la Ciudad Autónoma de Buenos Aires, Capital de la República
5 Argentina, el día NUEVE de MARZO del año DOS MIL SIETE, ante mí María
6 Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial número 1788,
7 COMPARACE: Dagmar MESSERER, argentina, nacida el 28 de mayo de 1.968,
8 hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Na-
9 cional de Identidad Número 20.383.892, Clave Única de Identificación Tributaria 27-
10 20383892-7, con domicilio especial en la Avenida Leandro N. Alem 1.134, Piso 10º,
11 de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- INTERVIE-
12 NE: por su propio derecho.- Y la compareciente EXPRESA: PRIMERO: Que la
13 Sociedad "BAYER SCHERING PHARMA AG", con domicilio en Müllerstrasse
14 178, 13353, Berlín, Alemania, le confirió con fecha 22 de enero de 2007 en dicho pa-
15 ís, un Poder, el cual mediante escritura número 14 de fecha 16 de febrero de 2007,
16 otorgada ante la Escribana Mariela Vanina Scardaccione, al folio 44, protocolo co-
17 rriente de este Registro Notarial interinamente a su cargo, fue incorporado y transcrip-
18 to al mismo, cuya primera copia tengo para este acto a la vista, doy fe y en lo perti-
19 nente transcribiré en la presente.- SEGUNDO: Manifiesta bajo juramento que el refe-
20 rido poder se encuentra plenamente vigente en virtud de no haberle sido revocado,
21 suspendido ni limitado en ninguna de sus partes.- TERCERO: En consecuencia, DI-
22 CE: Que en uso de la facultad conferida SUSTITUYE PARCIALMENTE el poder
23 mencionado a favor de Carlos Reinaldo OLARTE y/o James Ian RAISBECK, al
24 solo y único objeto de que en nombre y representación de la Sociedad "BAYER
25 SCHERING PHARMA AG", y actuando en forma individual, indistinta y/o alterna-



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damente, se presente exclusivamente ante las autoridades de COLOMBIA que co-
rrespondan y realicen los actos enumerados en el citado poder y con las facultades que
surgen del mismo, el que transcripto en lo pertinente dice: "FOLIO 44.- PRIMERA
COPIA.- ESCRITURA NÚMERO: CATORCE.-- En la Ciudad Autónoma de
Buenos Aires, Capital de la República Argentina, el día DIECISEÍS de FEBRERO del
año DOS MIL SIETE, ante mí ..., Escribana Autorizante, ..., COMPARECE: Dagmar
MESSERER, argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y
Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número
20.383.892, Clave Única de Identificación Tributaria 27-20383892-7, domiciliada
legalmente en la Avenida Leandro N. Alem 1.134, Piso 10º, de esta Ciudad de Buenos
Aires.- La compareciente es mayor de edad.- INTERVIENE: por su propio derecho.-
Y la compareciente EXPRESA: Que a los efectos que hubiere lugar, solicita de mí, la
Autorizante, LA INCORPORACIÓN y TRANSCRIPCIÓN en este protocolo del
PODER que le fuera conferido en Berlín, Alemania, el 22 de enero de 2007, por la
Sociedad "BAYER SCHERING PHARMA AG", con domicilio en Müllerstrasse 178,
13353, Berlín, Alemania, sobre cuya plena vigencia responde la requirente bajo jura-
mento.- Yo, la Autorizante, hago constar: a) Que el instrumento de poder cuya incor-
poración y transcripción a este protocolo solicita la compareciente, se encuentra ex-
tendido en idioma castellano, certificadas las firmas por notario en idioma alemán,
debidamente legalizado en idioma alemán (Sello de Apostilla de la Convención de La
Haya del 5 de octubre de 1961) y traducido en lo pertinente al idioma nacional por la
Traductora Pública Laura Thieberger.- b) Que la compareciente en virtud de lo mani-
festado tiene interés legítimo en su requerimiento.- En consecuencia, me hace entrega
en este acto del original del instrumento de poder relacionado con su respectiva tra-
ducción al idioma nacional, el que agrego a la presente y transcripto dice: "MOE-

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[Circular stamp: MARIA STOLINA LASARTE]

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1 LLER & CO. (Sigue aclaración en idioma inglés) - PODER Los abajo firmante/s
2 BAYER SCHERING PHARMA AG domiciliados en Müllerstrasse 178 13353 Berlín
3 - Alemania declaran por el presente otorgar a Dagmar MESSERER poder general am-
4 plio y suficiente para recabar de las autoridades ..., sud y centroamericanas ... que co-
5 rrespondan, la obtención de patentes de invención, el registro y la renovación de mar-
6 cas y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo
7 efecto los faculta/n para llevar a cabo ante dichas autoridades todas las gestiones nece-
8 sarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones,
9 protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explota-
10 ciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, per-
11 cibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier
12 orden. Por otra parte, les confieren mandato para que en su nombre y representación
13 puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o
14 en el futuro tuvieran ..., en Sudamérica, Centroamérica ..., con motivo de su nombre,
15 marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos
16 de propiedad intelectual que actualmente posean o adquieran en lo sucesivo; promover
17 juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales;
18 contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos
19 que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposi-
20 ción u otros en que fueran parte como actores o demandados, defender el nombre, las
21 marcas, patentes y modelos y/o de derechos de propiedad intelectual y/o nombres de
22 dominio, haciendo las protestas del caso o diciendo de nulidad. Al efecto, podrán pre-
23 sentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier auto-
24 ridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de
25 cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir



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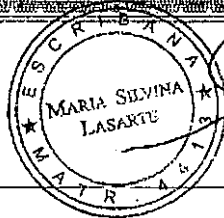
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a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar,
someter a arbitraje o mediación, hacer renunciaciones, exigir y dar cauciones, pedir embar-
gos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los
bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar ju-
ramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar
todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán
asimismo substituir el presente poder en todo o en parte.- Dado y firmado en Berlín
(Sigue fecha en idioma inglés). Bayer Schering Pharma AG (Sigue texto en idioma
inglés). ppa. Sigue una firma ilegible. (Aclarado:) Dr. Noeske-Jungblut. ppa. Sigue
otra firma ilegible. (Aclarado:) Dr. Klose". ES COPIA FIEL, doy fe.- En hoja adjunta
consta la certificación notarial de las firmas obrantes en el poder en idioma alemán,
efectuado el 22 de enero de 2007 por el Escribano Dimitri Rempen, de Berlín, Alema-
nia, y a continuación consta la respectiva legalización de la firma y sello del nombra-
do Notario (Sello de Apostilla de la Convención de La Haya del 5 de octubre de
1961), en idioma alemán, efectuada por el Presidente del Tribunal Regional de Berlín,
Alemania.- En hojas adjuntas sigue la referida traducción al idioma nacional la que
transcripta textualmente, dice: "TRADUCCIÓN PUBLICA - (Sobre papel con mem-
brete de "MOELLER y CO" - América Latina - Agentes de la Propiedad Intelectual -
figura un Poder otorgado por la Sociedad "BAYER SCHERING PHARMA AG", con
sede en Berlín, Alemania, redactado en idioma nacional, luego del que aparecen los
siguientes textos, que traducidos dicen:) "BAYER SCHERING PHARMA AG" -
Patentes y licencias - (Firmado y Aclarado:) pp Dr. Noeske-Jungblut - pp (Firmado y
Aclarado:) Dr. Klose.- La versión en inglés es para su información únicamente.- Re-
gistro de Actas N° R 17/2007.- Me he referido a la prohibición de intervención según
el artículo 3, párrafo 1, N° 7, de la Ley de Certificaciones. Mi pregunta de si ha existi-

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do una intervención previa en el sentido de la norma me fue contestaba por la negati-
va.- Las firmas trazadas ante mi por el Dr. Walter Klose, que nació el 26 de diciembre
de 1952, y de la Dra. Chistiane Noeske-Jungblut de soltera Noeske, que nació el 26 de
junio de 1957 – Ambos de mi personal conocimiento – Ambos con domicilio comer-
cial en 13353 Berlín, Müllerstrasse 178 son auténticas, de lo que doy fe.- Al mismo
tiempo certifico en base a que tuve a la vista en el día de hoy las actas del Registro de
Comercio del Tribunal de Primera Instancia de Charlottenburg, N° de Registro HR B
283, que la Sociedad “Bayer Schering Pharma Aktiengesellschaft”, con sede en Ber-
lín, está inscripta con el número mencionado arriba en el Registro de Comercio y que
la arriba mencionada Dra. Noeske-Jungblut y el arriba mencionado Dr. Walter Klose
están facultados en su carácter de mandatarios a representar en forma conjunta a la
Sociedad “Bayer Schering Pharma Aktiengesellschaft” de Berlín. Berlín, 22 de enero
de 2007.- El escribano (firma ilegible) y liquidación de derechos. (Hay un sello en
oblea sobre precinto:) Dimitri Rempen, Escribano de Berlín.- 9101ª E-F.- APOSTI-
LLA – (Convención de La Haya del 5 de Octubre de 1961) - País: República Federal
de Alemania - Este instrumento público fue firmado por Dimitri Rempen, actuando en
su carácter de escribano de Berlín, estando provisto del sello del escribano.- Certifica-
do en Berlín, el 24 de enero de 2007, por el Presidente del Tribunal Regional de Ber-
lín, con el N° 9101 a E-F 536/07 - Sello (hay un sello:) el Presidente del Tribunal Re-
gional de Berlín – Firma el Funcionario autorizado (firmado y aclarado:) Holldorf –
Juez Principal del Tribunal Regional.- ES TRADUCCIÓN FIEL de las partes perti-
nentes en los idiomas alemán e inglés del documento que se acompaña, que he vertido
al idioma nacional, en Buenos Aires, a 6 de febrero de 2007.- Hay una firma ilegible.
Hay un sello que dice: “LAURA THIEBERGER – MATRÍCULA DE TRADUCTO-
RES ALEMÁN – FRANCÉS – Tomo II Folio 254 (Cap.) Tomo III – 98 – (La Plata) –



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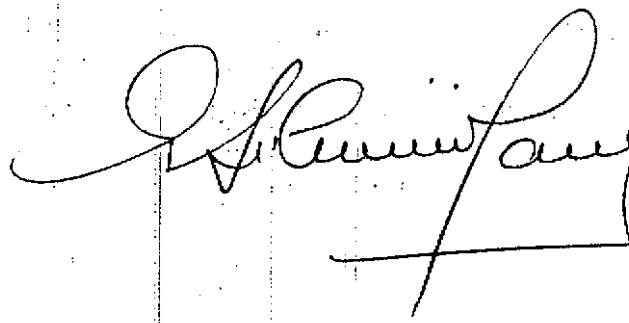
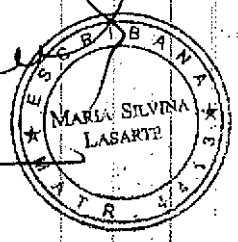
INGLÉS – Tomo III: Folio 14 (Cap.) – Tomo III Folio 329 (La Plata) – COLEGIO
DE TRADUCTORES PÚBLICOS N° 173”.- ES COPIA FIEL, doy fe.- A continua-
ción hay un sello que dice: “COLEGIO DE TRADUCTORES PÚBLICOS DE LA
CIUDAD DE BUENOS AIRES Corresponde a la Legalización N° T4-3278/07. Sigue
una firma ilegible: Esteban Santiago Allegretti”.- ES COPIA FIEL, doy fe.- Al dorso
en el margen superior hay un sello timbrador ...”.- A continuación sigue la legaliza-
ción de la firma de la nombrada traductora, ...”.- ES COPIA FIEL, doy fe.- En este
estado la compareciente DICE que en la forma expresada deja INCORPORADO y
TRANSCRIPTO en este Protocolo el Poder que agrego a la presente, solicitando de
mí, la Escribana Autorizante, expida primera copia de la presente para la nombrada
apoderada Dagmar MESSERER.- Constancias Notariales: Identidad de la compare-
ciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de la
Autorizante.- ...- LEO esta escritura a la compareciente, quien así la otorga y en prue-
ba de conformidad, la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MA-
RIELA VANINA SCARDACCIONE. Escribana. Está mi sello. CONCUERDA con
su escritura matriz que pasó ante mí, al folio 44 del Registro Notarial número 1788,
interinamente a mi cargo.- PARA LA APODERADA expido la presente PRIMERA
COPIA en tres (3) sellos de actuación notarial numerados correlativamente desde el
número N 007376153 al presente inclusive, que sello y firmo en la fecha y lugar de su
otorgamiento, doy fe.- Sigue una firma ilegible y un sello que dice: Mariela V. Scar-
daccione – Escribana – Mat. 4527.”.- ES COPIA FIEL, de las partes pertinentes de la
escritura de referencia, doy fe.- **CUARTO:** Finalmente la compareciente expresa: a)
Que el presente otorgamiento no significa renunciar al ejercicio de las facultades sus-
tituidas; y b) Que los nombrados apoderados sustitutos no podrán sustituir el presente
poder en ninguna de sus partes.- Constancias Notariales: Identidad de la Compare-

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1 ciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de
2 la Autorizante.-Yo, la Escribana Autorizante impongo y advierto a la compareciente, a
3 tenor de lo dispuesto en el artículo 77 inciso h) de la Ley Orgánica Notarial Número
4 404, respecto de los alcances y consecuencias de las cláusulas contenidas en la presen-
5 te escritura y del derecho de leer por sí este instrumento.- LEO esta escritura a la
6 compareciente, quien así la otorga y en prueba de conformidad la firma ante mí, doy
7 fe.- Dagmar MESSERER. Ante mí: MARIA SILVINA LASARTE. Escribana. Está
8 mi sello. CONCUERDA con su escritura matriz que pasó ante mí, al folio 85 del Re-
9 gistro Notarial número 1788, a mi cargo. PARA LA PODERDANTE expido la pre-
10 sente PRIMERA COPIA en cuatro (4) sellos de actuación notarial numerados corre-
11 lativamente desde el número N 007422051 al presente inclusive, que sello y firmo en
12 la fecha y lugar de su otorgamiento, doy fe.-



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COLEGIO DE ESCRIBANOS
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BUE - 26

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COLEGIO DE ESCRIBANOS
CIUDAD DE BUENOS AIRES

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República

Argentina, en virtud de las facultades que le confiere la ley vigente, **LEGALIZA** la firma
y sello del escribano **MARIA SILVINA LASARTE**

obrantes en el documento anexo, presentado en el día de la fecha bajo

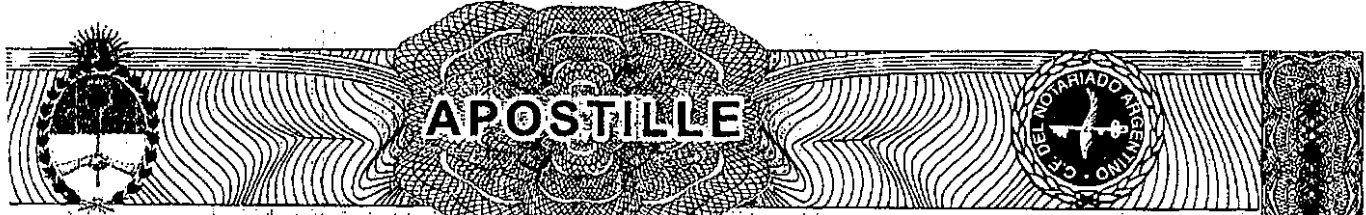
el N° **070312117346/0** La presente legalización no juzga sobre

el contenido y forma del documento.

Buenos Aires, Lunes 12 de Marzo de 2007



[Handwritten signature]
ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA



REPUBLICA
ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00115229

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por EDDA ENRIQUETA SINELLI

3. Quien actúa en calidad de CONSEJERA

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS
AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 12/03/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 070312054713

10. Firma

ESC. HECTOR R. NOVARO
COLEGIO DE ESCRIBANOS
CONSEJERO



COLEGIO DE ESCRIBANOS
CIUDAD DE BUENOS AIRES