Table I. Specific Rotation and Melting Points for the Compounds Studied

Compound	Isomer	$[\alpha]^{22}D$, deg	c	Medium	Mp, °C	Lit.[3] $[\alpha]^{25}D$, deg	c	Medium
Quinuclidinol	(−)	−1.8	5	H_2O		−0.3	7	H_2O
(+)-camphorsulfonate	(+)	+20.2[a]	3	H_2O		+20.0[a]	7	H_2O
Quinuclidinol	(−)	−44.7	3	1 *M* HCl		−43.8	3	1 *M* HCl
	(+)	+16.0[a]	3	1 *M* HCl				
Quinuclidinyl benzilate	(−)	−33.8	0.5	0.2 *M* HCl	189–190			
	(+)	+32.6	0.5	0.2 *M* HCl	188–190			
	(±)				166–168			

[a]Partially resolved.

Table II. Pharmacological Effects for Different Doses of the Isomers of 3-Quinuclidinyl Benzilate

Isomer	Dose, mg/kg	Ataxia	Nonretreating	Salivation and heart rate	Number of experiments
Racemate	0.01	+	+	+	2 (lit.[6])
Levo	0.01	+	+	+	3
Dextro	0.01	−	−	−	1
Dextro	0.05	−	−	−	1
Dextro	0.1	−	−	−	1
Dextro	0.2[a]	+	2+/1−[b]	1+/2−[c]	3
Dextro	0.3	+	+	−	2
Dextro	0.5	+	+	−	1
Dextro	1.0	+	+	+	1

[a]Estimated threshold dose for central effects. [b]Two out of three animals gave a positive effect. [c]One out of three animals gave a positive effect.

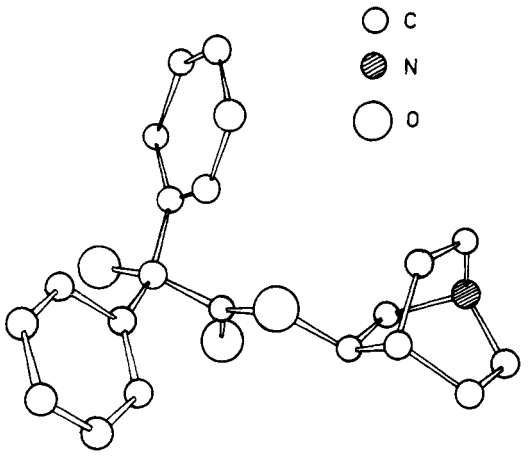

Figure 1. A perspective drawing of the (*R*)-(−)-3-quinuclidinyl benzilate molecule as it is found in crystals of the hydrobromide.

situated anticlinal to the nitrogen atom, the torsion angle being +125° between the plane O–C–C and the plane C–C–N.

The results of the pharmacological tests are illustrated in Table II. It can be concluded that the levoratory QB is at least 20 times more potent than its (+) isomer. The test method is not accurate enough to distinguish between the potency of the (−) isomer and the racemate. Since the maximum impurity of the (−) isomer in the (+) isomer is 1.8% calculated from the optical rotation measurements, the effect of the (+) isomer might be attributable to the impurity. Thus it is not possible to say that the compound with the *S* configuration lacks activity. However, the results agree well with those of Sternbach and Kaiser[3,4] with respect to the fact that the nonquaternized drugs show a difference in potency between the enantiomers derived from asymmetric alcohols, while the quaternized drugs do not. This behavior might then be unique for esters of quinuclidine.

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Terpene Compounds as Drugs. 11. Anabolic 19-Nortestosterone Terpenoates

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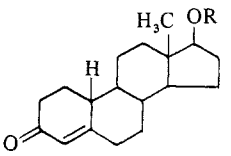
As part of our program in the field of terpene compounds as drugs,[1,2] we have prepared for preliminary anabolic testing[3] a number of esters of 19-nortestosterone with acyclic and cyclic terpenyl acids. The new substances (Table I) were obtained by allowing the steroid alcohol to

Table I. Esters of 19-Nortestosterone



Compd	R	Method	Yield, %[a]	Mp, °C	R_f (tlc)	Formula[b]
1	Geranoyl	A	38	Oil	0.82	$C_{28}H_{40}O_3$
2	Homogeranoyl	A	40	Oil	0.85	$C_{29}H_{42}O_3$
3	Geranylacetyl	A	68	Oil	0.85	$C_{30}H_{44}O_3$
4	Nerylacetyl	A	62	Oil	0.82	$C_{30}H_{44}O_3$
5	Citronelloyl	A	57	Oil	0.81	$C_{28}H_{42}O_3$
6	*trans,trans*- and *cis,trans*-Farnesoyl[c]	A	43	Oil	0.84	$C_{33}H_{48}O_3$
7	*trans,trans*- and *cis,trans*-Homofarnesoyl[d]	A	74	Oil	0.85	$C_{34}H_{50}O_3$
		B	85			
8	*trans,cis*- and *cis,cis*-Homofarnesoyl[d]	A	66	Oil	0.85	$C_{34}H_{50}O_3$
9	*trans,trans*- and *cis,trans*-Farnesylacetyl[e]	A	77	Oil	0.87	$C_{35}H_{52}O_3$
		C	77			
10	*trans,cis*- and *cis,cis*-Farnesylacetyl[e]	A	67	Oil	0.85	$C_{35}H_{52}O_3$
11	α-Cyclogeranoyl	A	60	121-123	0.80	$C_{28}H_{40}O_3$
12	β-Cyclogeranoyl	A	70	134-135	0.79	$C_{28}H_{40}O_3$
13	Dihydrocyclogeranoyl	A	17	170-172	0.83	$C_{28}H_{42}O_3$
14	α-Bicyclofarnesoyl	A	38	Wax	0.84	$C_{33}H_{48}O_3$

[a] Chromatographed product. [b] All compounds were analyzed for C, H and the analytical values were within ±0.4% of the theoretical values. [c] The first configurational designation refers to the 3,4 double bond, the second to the 7,8 double bond. [d] The first configurational designation refers to the 4,5 double bond, the second to the 8,9 double bond. [e] The first configurational designation refers to the 5,6 double bond, the second to the 9,10 double bond.

react with the appropriate acid chlorides in $CHCl_3$ solution at room temp in the presence of a small excess of pyridine (method A). Alternatively, esters **7** and **9** have also been prepared from the corresponding terpenyl acid (method B) and anhydride (method C), respectively. Purification from traces of 19-nortestosterone and terpenyl acids was performed by chromatography on alumina. We wish to point out that, in accordance with the mode of formation, esters **6-10** must be regarded as mixtures of the possible configurational isomers, due to the presence of olefinic bonds around which a cis,trans stereoisomerism may occur. In these cases, the physical constants given in Table I are to be considered as merely indicative.

Biological Results. Anabolic potency and duration of action were estd by the myotrophic-androgenic assay method of Hershberger, *et al.*[3] Male Sprague-Dawley rats were castrated at 21 days of age and received, on the day of surgery, a single subcutaneous injection of the test compd; 1, 2, 3, 4, 6, 8, and 10 weeks from the start of treatment, the animals were sacrificed and the levator ani (LA), ventral prostata (VP), and seminal vesicles (SV) were removed and weighed. The tissue:body wt ratio (mg of tissue/100 g of body wt) was taken as the end point (the results are given in Table II). In order to compare the esters for potency and duration of anabolic and androgenic activity the increases of the organ weights over the untreated castrate controls were plotted for each of the esters *vs.* the period of weeks studied and the areas under the levator ani (A_{LA}), ventral prostata (A_{VP}) and seminal vesicles (A_{SV}) curves were calcd at the various times. Differences $A_{LA} - A_{VP}$ and $A_{LA} - A_{SV}$ are given in Table III. 19-Nortestosterone phenylpropionate was used as ref std in all the experiments.

Many of the esters of 19-nortestosterone with acyclic terpenyl acids (**1-10**) produced a marked myotrophic-androgenic response as measured in the first 3 weeks (Tables II and III). At this time, esters **4**, **7**, **8**, and **10** appeared to

Table II. Long-Term Anabolic-Androgenic Assay

	1 week			2 weeks			3 weeks			4 weeks			6 weeks			8 weeks			10 weeks		
Compd[a]	VP[b]	SV[b]	LA[b]	VP	SV	LA	VP	SV	LA	VP	SV	LA	VP	SV	LA	VP	SV	LA	VP	SV	LA
1	2.1	12.4	5.9	0.0	1.1	5.2	0.0	0.0	0.0												
2	30.8	73.4	22.9	7.6	28.4	32.8	0.9	3.2	15.5												
3	21.8	66.6	21.3	13.0	39.4	19.5	4.4	10.2	16.8												
4	67.4	117.0	57.0	87.4	140.9	62.7	57.8	111.0	61.0	46.3	130.7	71.5	45.8	58.2	98.0	24.4	30.3	50.2	15.3	32.3	42.0
5	15.0	47.4	23.0	9.6	41.0	30.1	0.0	4.2	14.7												
6	0.0	2.5	5.1	0.2	0.0	3.6	0.0	0.0	3.9												
7	21.3	42.4	39.9	8.7	17.9	27.3	7.4	15.4	30.5	12.0	46.4	51.2	19.3	50.3	52.1	13.1	28.7	49.2	5.3	11.3	42.0
8	43.1	58.0	43.0	46.4	67.4	47.7	26.4	55.0	36.0	35.3	55.7	72.5	26.4	41.2	48.0	15.4	25.2	42.2	1.2	12.8	0.0
9	4.6	17.1	2.9	7.3	8.9	11.2	2.1	9.1	19.3												
10	34.1	65.0	45.0	19.4	39.9	40.2	21.2	40.0	47.0	30.3	36.7	56.5	19.8	50.2	43.0	12.3	28.7	43.2	1.8	14.3	38.0
11	0.0	2.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0												
12	0.0	1.1	0.0	0.0	0.0	0.2	0.6	0.2	0.2												
13	0.0	0.0	4.7	0.0	1.7	0.0	0.8	0.0	0.0												
14	1.1	2.5	4.3	0.0	0.0	0.0	0.6	0.7	1.5												
19-Nortestosterone phenylpropionate	31.0	59.4	22.9	46.0	124.5	44.2	52.7	111.3	26.3	14.8	21.8	18.1	2.7	5.6	1.6						

[a] Single subcutaneous injection of 8.0 mg/rat (expressed as 19-nortestosterone) in 0.5 ml of olive oil. [b] Milligram increases of LA muscle, VP, and SV over control; average of 10 animals/group.

Table III. Differences between Areas of the Increases in LA Muscle, VP, and SV (Values Calculated from Table II)

Compd	3 weeks		6 weeks		10 weeks	
	$A_{LA} - A_{VP}$	$A_{LA} - A_{SV}$	$A_{LA} - A_{VP}$	$A_{LA} - A_{SV}$	$A_{LA} - A_{VP}$	$A_{LA} - A_{SV}$
1	+18.0	−4.8				
2	+49.2	−79.9				
3	+24.4	−123.8				
4	−67.0	−326.4	+116.2	−474.4	+377.2	−295.8
5	+71.7	−60.1				
6	+20.9	+16.3				
7	+97.5	+28.9	+303.8	+62.0	+587.2	+209.0
8	+12.0	−88.4	+176.4	−43.4	+324.4	+ 12.6
9	+21.6	−13.6				
10	+89.2	−32.4	+240.0	+19.6	+482.4	+110.6
11	0.0	−5.4				
12	0.0	−1.8				
13	+8.6	+6.0				
14	+7.3	+4.4				
19-Nortestosterone phenylpropionate	−46.2	−318.6	−64.9	−422.7		

be the most interesting while **2**, **3**, **5**, and **9** were lower in potency and **1** and **6** were practically inactive. The activities have been made more evident by reporting in the same tables the data for the similarly tested 19-nortestosterone phenylpropionate. On assaying esters **4**, **7**, **8**, and **10** for a further 7 weeks, the activity of 19-nortestosterone homofarnesate (**7**) was significantly higher than that of the other esters. Ester **7** was characterized by a good myotrophic (anabolic) response at each time period (as measured by LA muscle weight increase), by a concurrent low androgenic response (as measured by the increase in VP and SV), and by the duration of the anabolic effect. Ester **7** appears to peak in myotrophic activity at 6 weeks, and the phenylpropionate ester in 2 weeks, as can be seen in Table II and Figure 1. At 10 weeks the anabolic activity of **7** is still high, whereas that of the phenylpropionate ester practically disappears at 6 weeks. At this time, the androgenic response of **7** was only minimal. Both dissociation of myotrophic from androgenic activity and duration of the myotrophic response of **7** are better evidenced by the differences $A_{LA} - A_{VP}$ and $A_{LA} - A_{SV}$ given in Table III.

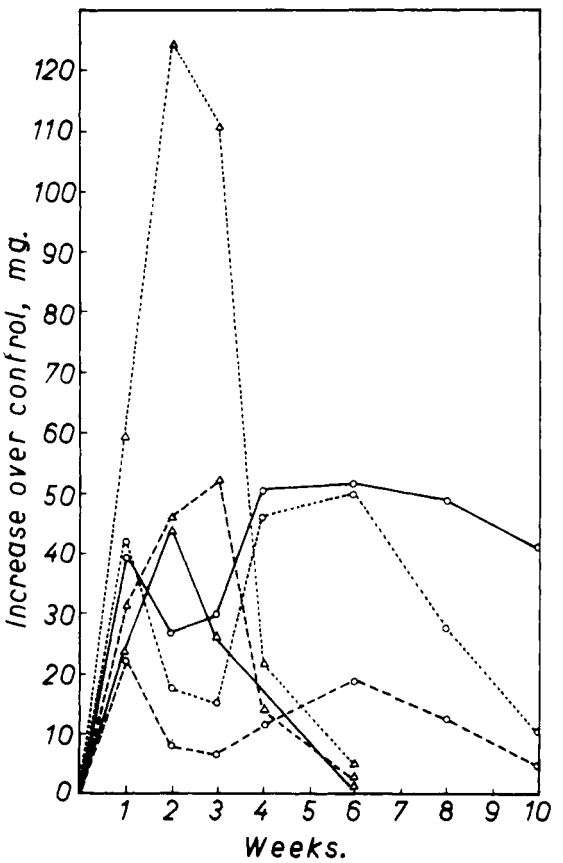


Figure 1. LA muscle, VP, and SV response to a single subcutaneous administration. 19-Nortestosterone homofarnesate (**7**): LA muscle (—○—○—), VP (——○———○——), and SV (- - ○ - - - ○ - -); 19-nortestosterone phenylpropionate: LA muscle (—△—△—), VP (——△——△——), and SV (- - △ - - - - △ - -).

On the basis of these results, 19-nortestosterone homofarnesate (**7**) seems to meet the requirements pointed out by Scribner, *et al.*,[4] according to whom optimum rather than maximum lipophilicity and resistance toward hydrolysis are essential for an ester to be a good anabolic agent. This is consistent with the structure of homofarnesic acid, which was employed in preparing **7**, as this acid, due to the branching and to the particular configuration determined by cis,-trans stereoisomeric factors, presents some degree of steric hindrance.

Being very hindered and probably quite resistant to hydrolysis *in vivo*, all of the esters of 19-nortestosterone with cyclic terpenyl acids (**11-14**) were lacking in both anabolic and androgenic activity (Tables II and III). This finding supports the assumption that was made by Scribner, *et al.*,[4] for esters of this type.

Due to the promising results exhibited in the preliminary anabolic testing, ester **7** was submitted to more detailed physicochemical, pharmacological, and toxicological studies as well as to clinical trials. These studies will be the subject of forthcoming publications.

Experimental Section†

The intermediate acid chlorides were prepd as previously described.[2] 19-Nortestosterone esters are listed in Table I, and their prepn is illustrated by the following methods. Mode of formation and nmr evidenced that farnesoyl ester **6** consists of the trans,trans and cis,trans isomers, while the two homofarnesoyl esters **7** and **8** consist of the trans,trans and cis,trans, and of the trans,cis and cis,cis ones, respectively. Similarly, the two farnesylacetyl esters **9** and **10** consist of the trans,trans and cis,trans isomers, and of the trans,cis and cis,cis ones, respectively.

†Melting points are corrected and were taken on a Büchi capillary melting point apparatus. The R_f values were determined on glass chromatostrips coated with silica gel G Merck; the tlc was performed with C_6H_6-Me_2CO (80:20). The spots were detected with a 1% soln of vanillin in concd H_2SO_4. Nmr spectra were taken with a Varian spectrometer Model A-60 A operating at 60.00 Mcps.

Method A. 19-Nortestosterone 17β-Geranate (1). A soln of geranoyl chloride (3.08 g, 0.0165 mole) in $CHCl_3$ (30 ml) was dropped at room temp for 10 min into a stirred soln of 19-nortestosterone (4.11 g, 0.015 mole) and dry pyridine (1.5 g, 0.019 mole) in $CHCl_3$ (70 ml). The mixt was stirred overnight, dild with $CHCl_3$ (200 ml), and washed (2% HCl, H_2O) until neutral. After drying ($MgSO_4$), the solvent was evapd, and the residue was chromatographed on neutral, activity grade I alumina. Elution with C_6H_6 and C_6H_6–Me_2CO gave 2.42 g of pure **1**.

Method B. 19-Nortestosterone 17β-*trans,trans*- and *cis,trans*-Homofarnesate (7). *Trans,trans*- and *cis,trans*-homofarnesic acid[2] (2.7 g, 0.01 mole) and 19-nortestosterone (1 g, 0.0036 mole) were heated under N_2 for 3 hr at 200°. After cooling, the reaction mixt was taken up in Et_2O (100 ml) and washed repeatedly with 5% Na_2CO_3. The organic layer was washed (H_2O) until neutral and dried ($MgSO_4$), and the solvent was evapd. The residue was chromatographed as described in method A to give 1.57 g of pure **7**.

Method C. 19-Nortestosterone 17β-*trans,trans*- and *cis-trans*-Farnesylacetate (9). Farnesylacetic anhydride[1] (3.06 g, 0.006 mole) was added dropwise at room temp for 10 min to a soln of 19-nortestosterone (0.8 g, 0.003 mole) in dry pyridine (3 ml). The mixt was stirred overnight, dild with Et_2O (30 ml), and washed (1% NaOH, 2% HCl, H_2O) until neutral. Evapn of the solvent and chromatog as described in method A furnished 1.2 g of pure **9**.

Acknowledgments. The authors wish to thank Dr. R. Perego for performing the microanalyses, Dr. T. Bruzzese and Mr. O. Boniardi for assistance in preparing the compounds, and Mr. C. Franco for assistance in carrying out the biological tests.

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New Compounds

Terpene Compounds as Drugs. 14. Terpenyl Carbamates as Central Nervous System Depressants

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The well-known anticonvulsant properties of several carbamate esters, together with our interest in the terpene field, have led us to synthesize a number of terpenyl carbamates (Table I) for a pharmacological evaluation of their CNS activity.

All the compounds were tested orally for CNS activity in mice, using meprobamate as reference standard. As can be seen from Table II, which reports the most interesting results, all the compounds caused CNS depression, which appeared as decrease in spontaneous motility[1] and body muscle tonus, motor incoordination, and loss of righting reflex. The most active compound was **1**, which in addition exhibited a marked anticonvulsant action against maximal electroshock (MES) and pentylenetetrazole (Met) seizures.[2] This effect, however, was less lasting than that of meprobamate. Unlike the standard, the new substances failed to potentiate the hexobarbital-induced sleep, as well as to prevent aggressive behavior induced by L-dopa.[3] None of the compounds showed central analgetic activity (tail-pinch test).[4]

Table I. Terpenyl Carbamates. $ROCONH_2$

Compd	R	Yield, %	Bp (mm) or mp, °C	Formula[a]
1	Prenyl	62[b]	45–46	$C_6H_{11}NO_2$
2	Homoprenyl	76.8[c]	69–70	$C_7H_{13}NO_2$
3	Citronellyl	63[d]	122–123 (0.5)	$C_{11}H_{21}NO_2$
4[e]	Geranyl	68.2[d]	110–117 (0.02)	$C_{11}H_{19}NO_2$
5	Neryl	53.8[d]	110–120 (0.06)	$C_{11}H_{19}NO_2$
6	Farnesyl	46.1[d]	144–145 (0.03)	$C_{16}H_{27}NO_2$

[a] All compds were analyzed for C, H, and N; the analytical values were within ±0.4% of the theoretical values. [b] Recrystd from petroleum ether (bp 40–70°). [c] Recrystd from cyclohexane. [d] Once distd. [e] Thiele, *et al.*,[5] report bp 112–115° (0.01 mm).

Table II. Pharmacological Results

Compd	Approx LD_{50}, mg/kg po	Anticonvulsant act. Met,[a] ED_{50}, mg/kg po	Anticonvulsant act. MES,[b] ED_{50}, mg/kg po	Spontaneous motility decrease, ED_{50}, mg/kg po
1	>800	87	90	288
2	>800	400	207	261
3	>800	460	230	395
4	>800	530	>800	>400
5	>800	365	570	291
6	>800	285	435	207
Meprobamate	750	62	182	203

[a] 125 mg/kg ip. [b] Ear electrodes, 10 mA, 0.2 sec.

Experimental Section†

General Procedure. Phenyl chloroformate (15.65 g, 0.1 mole) was added over 20 min to a stirred soln of the appropriate alcohol (0.1 mole) in dry pyridine (50 ml) at 5–10°. After 2 hr stirring at room temp, the mixt was poured into ice H_2O and extd (Et_2O). The Et_2O soln of the carbonate ester was washed (H_2O, 5% HCl, satd $NaHCO_3$, H_2O), dried (Na_2SO_4), and then added dropwise with stirring to liquid NH_3. After 2 hr the excess NH_3 was allowed to evaporate at room temp, and the residue was taken up in Et_2O, washed (1 *N* NaOH, satd NaCl), and dried (Na_2SO_4). Removal of the solvent afforded the crude product, which was purified as shown in Table I.

Acknowledgments. The authors wish to thank Dr. A. Gallazzi for performing microanalyses, Mr. E. Zugna for assistance in preparing the compounds, and Mr. A. Ghiorzi for carrying out the pharmacological tests.

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†Melting points were taken on a Büchi capillary melting point apparatus and are corrected; boiling points are uncorrected. Ir and nmr spectra were consistent with the assigned structures.