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Synthesis of Stereoisomeric Bornane and Norbornane Derivatives with Spasmolytic Activity

Synthese stereoisomerer Bornan- und Norbornanderivate mit spasmolytischer Wirkung

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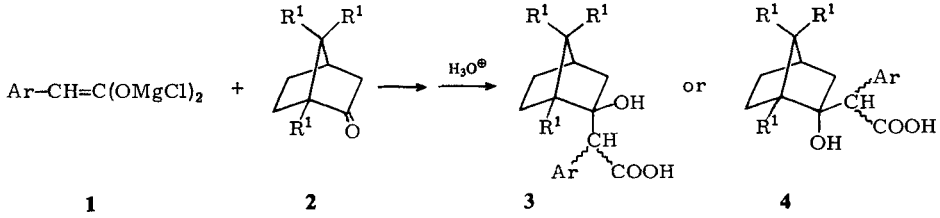
In previous studies[1,2] we found that the addition of *Ivanov* magnesium reagents **1** to camphor and norcamphor occurred either in the *endo* **3** or *exo* **4** position, depending on the experimental conditions.



1 **2** **3** **4**

By means of ^{13}C NMR spectroscopy the absolute configurations of the β-hydroxy acids **3** and **4** were determined[3].

Since it is well known that dialkylaminoesters of β-hydroxyacids possess biological activity[4,5,6] the esters of **3** and **4** with 2-N,N-dialkylaminoethanol were synthesized according to the following scheme[6]:

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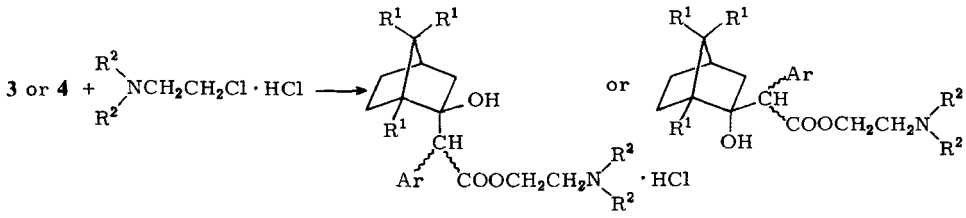

5 **6a-d** **7a-f**

In order to avoid the decomposition of the β-hydroxy acids to the corresponding arylacetic acids and ketones, occurring in alkaline medium[7], we modified the procedure and to a solution of **3** (or **4**) and **5** in i-PrOH, i-PrONa was added.

The spasmolytic activity of the newly synthesized compounds was studied on an isolated smooth muscle preparation-guinea pig ileum according to the standard procedure[8]. The dosage manifesting the maximum activity of the studied compounds was found to be 4 μg/ml Tyrode solution. At this dosage the contraction of the smooth muscle preparation caused by acetylcholine (**ACh**) – dosage 4 μg/ml was removed (see Table 1).

Table 1: *Hydrochlorides of exo- or endo-β-N,N-dialkylaminoethyl-(2-hydroxy-born/or norborn-/-2-yl)arylacetates*

Starting ketone 2	Compound*	R^1	R^2	Ar	Yield %	m.p.** °C	$[\alpha]_D^{20}$ (c=0.2, H_2O)	Formula	N % Calc.	N % Found	Spasmolytic activity %***
(±)camphor	**6a**	CH_3	CH_3	C_6H_5	42	184–186	–	$C_{22}H_{34}NO_3Cl$	3.5	3.9	71
(+)camphor	**6b**	CH_3	CH_3	C_6H_5	37	185–187	−29	$C_{22}H_{34}NO_3Cl$	3.5	3.9	96
(±)camphor	**6c**	CH_3	CH_3	p-$CH_3OC_6H_4$	30	192–194	–	$C_{23}H_{36}NO_4Cl$	3.3	3.6	90
(+)camphor	**6d**	CH_3	CH_3	p-$CH_3OC_6H_4$	31	189–193	−36	$C_{23}H_{36}NO_4Cl$	3.3	3.7	81
(±)camphor	**7a**	CH_3	CH_3	C_6H_5	50	178–180	–	$C_{22}H_{34}NO_3Cl$	3.5	3.2	92
(+)camphor	**7b**	CH_3	CH_3	C_6H_5	62	183–185	−62	$C_{22}H_{34}NO_3Cl$	3.5	3.7	47
(±)camphor	**7c**	CH_3	CH_3	p-$CH_3OC_6H_4$	40	174–176	–	$C_{23}H_{36}NO_4Cl$	3.3	3.6	47
(+)camphor	**7d**	CH_3	CH_3	p-$CH_3OC_6H_4$	80	183–185	−50	$C_{23}H_{36}NO_4Cl$	3.3	3.5	74
(±)norcamphor	**7e**	H	CH_3	C_6H_5	40	113–115	–	$C_{19}H_{28}NO_3Cl$	4.6	4.1	96
(±)norcamphor	**7f**	H	CH_3	p-$CH_3OC_6H_4$	47	104–106	–	$C_{20}H_{30}NO_4Cl$	3.6	3.9	100
(±)norcamphor	**7g**	H	C_2H_5	p-$CH_3OC_6H_4$	74	143–146	–	$C_{22}H_{34}NO_4Cl$	3.4	3.6	92

* All compounds are diastereoisomeric mixtures in a ratio according to[1,2].

**The compounds softened 5–10° below their mp and melted with decomp.

***$\frac{X}{Y} \cdot 100$, where Y – ACh-caused contraction of the smooth muscle preparation, X – extent of removal of the contraction caused.

Both the compounds obtained from pure enantiomer and from the racemic ketone possessed spasmolytic activity. No significant difference in the spasmolytic activity of the *exo* **3** and *endo* **4** derivatives of camphor was found when using **ACh** as spasmogenic substance. Compound **7f** demonstrated the highest spasmolytic activity. A comparative study of the *endo* and *exo* isomers of norbornanone could not be undertaken since it was impossible to obtain in preparative yields the ketone derivatives containing an ester group in the *endo* position, because of difficulties in their separation[2,9].

Having in mind literature data[4,5,6] concerning esters of β-hydroxy acids containing a diethylamino group, we synthesized compound **7g** and found that it possessed an even lower activity than its dimethylaminoethyl analogue **7f**.

A comparative study of the synthesized aminoesters using different spasmogens as well as a comparison of their activity with the activity of spasmolytics widely used in medical practice is now in progress.

Experimental Part

β-*hydroxyacids* **3** and **4** were prepared according to[1,2].

Hydrochlorides of exo- or *endo-β-N,N-dialkylaminoethyl-(2-hydroxy-born-2-yl)arylacetates* **6a–d**, **7a–d**; *exo-β-N,N-dialkylaminoethyl-(2-hydroxy-norborn-2-yl)arylacetates* **7e–g**

To 0.05 mole of **5** and 0.05 mole of **3** or **4** in 50 ml of isopropanol, 0.05 mole of i-PrONa was added. After boiling 36 h the NaCl precipitated was discarded, the filtrate concentrated and the corresponding hydrochlorides **6** or **7** crystallized upon addition of absol. ether. They were recrystallized from isopropanol. In the IR spectra (nujol) of all products, bands at 1740–1700 cm^{-1} (C=O) and 3410–3320 cm^{-1} (OH) were observed.

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