9. 5',6-Diformyl-2,2',3-trimethoxydiphenylether **(17)**

Methode a: Reaktionszeit 23 h. Das erhaltene Produktgemisch wurde sc getrennt. Kieselgel 70–230 mesh (Macherey und Nagel), Säule: 70 × 2,5 cm, Mobile Phase: Chloroform, 1. Fraktion: 1,55 g Veratrumaldehyd, 2. Fraktion: Diphenylether **17**, Ausb.: 0,65 g (10 % d.Th.), Schmp.: 80–85° (Ether/Cyclohexan). $C_{17}H_{16}O_6$ (316,31) Ber. C 64,6 H 5,10 Gef. C 64,3 H 5,25. UV (MeOH): λmax (log ε) = 222 (4,47), 276 nm (4,34). NMR ($CDCl_3$): δ (ppm) = 10,15; 9,67 (2s, 2H, CHO); 7,79–6,81 (m, 5H, aromat. H); 4,02; 3,95; 3,68 (3s, 9H, OCH_3).

Methode b: Schmelztemp. 190°. Das Substanzgemisch wurde kugelrohrdestilliert. Dabei gingen bei 0,3 Torr bis 200° 3 g Veratrumaldehyd und 0,65 g Diphenylether **17** (10 % d.Th.) über (Ausbeutebest. NMR-spektroskopisch).

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[Ph 629]

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Synthesis of Vinca Alkaloids and Related Compounds, XV[1)]

A New Synthetic Route to (+)-Vincaminic and (+)-Apovincaminic Esters

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Esters of types **7** and **8**, possessing excellent vasodilating effects, have been prepared. A method has been found for the resolution of methyl ester **7c**. A new method is described for the preparation of the lactam (+)-**10** and its conversion to the oxime (+)-**11**, from which (+)-vincamine **(1a)** and the (+)-apovincaminic esters **2a,b** were synthesized.

0365-6233/83/0707-0629 $ 02.50/0

Über die Synthese von Vinca-Alkaloiden und verwandten Verbindungen, 15. Mitt.: Ein neuer Weg zur Synthese von (+)-Vincaminsäure- und (+)-Apovincaminsäureestern

Neue, beträchtliche gefäßweiternde Wirkung zeigende Verbindungen von Typ **7** und **8** wurden hergestellt und die Enantiomere des Methylesters **7c** getrennt. Das mit der neuen Methode synthetisierte (+)-**10** Laktam und das (+)-**11** Oxim lieferten das (+)-Vincamin **(1a)** und die (+)-Apovincaminsäureester **2a,b**.

The significant therapeutical value[4] of (+)-vincamine **(1a)**[3a-c] and its derivatives, e.g. Cavinton® **(2b)**[3a-c], inspired several research groups on the elaboration of an industrially feasible total synthesis of these compounds. The starting material of our previously described vincamine synthesis is the iminium salt **3** described by *Wenkert*[5] and the enamine **4** obtained upon the effect of bases from the above[2d,e]. The latter compound can also be prepared by more recent syntheses[2e,6].

As reported, enamine **4** can be alkylated with good yields in position 1 by electrophilic olefins. The reaction was carried out in methylene chloride at room temp., and the adducts were isolated generally in form of well crystallizing perchlorates **6a–h** (Table 1).

Table 1: *Physical data of* **6c–h** *perchlorates*

Compounds	Mp.[°C] Solvent	Yield [%]	IR (KBr), [cm^{-1}] Ind. NH	Ester CO	C=N	Molecular Formula M.w.	Calc./Found. C	H	N
6c	188–189 (MeOH)	87	3600	1742	1630 1540	$C_{21}H_{27}N_2O_6Cl$ 438.90	57.5 57.4	6.20 6.32	6.4 6.5
6d	198–199 (EtOH)	79	3590	1730	1630 1538	$C_{22}H_{29}N_2O_6Cl$ 452.92	58.3 58.4	6.45 6.42	6.2 6.5
6b	163–165 (i-BuOH)	76	3620	1730	1618 1522	$C_{24}H_{33}N_2O_6Cl$ 480.98	59.9 59.7	6.91 6.97	5.8 5.8
6g	148–150 (i-PrOH)	83	3250	1710	1620 1530	$C_{24}H_{33}N_2O_6Cl$ 480.98	59.9 59.8	6.91 6.75	5.8 5.9
6h	194–195 (i-PrOH)	77	3360	1710	1618 1525	$C_{24}H_{33}N_2O_6Cl$ 480.98	59.9 58.9	6.91 6.82	5.8 6.0

We have shown that during catalytic hydrogenation of the iminium salts **6a,b** the increasing bulkiness of group R^1 favours the formation of the products **7a,b**, which contain the 1-ethyl group and the 11b-H atom in *cis* position[2e].

The present investigations indicate that in hydrogenation of the iminium salts **6c–h** in methanol stereoselectivity is also proportional to the bulkiness of the group R^2 (Method A). It was also found that stereoselectivity depends on the pH of the medium as well as on the solvent applied. Significant stereoselectivity can be attained if the iminium salts **6c–h** are hydrogenated in DMF in the presence of Pd-C (Method B). Under such conditions *cis* esters of type **7** are obtained as main product with no regard to the bulk of group R^2 (Table 2).

Table 2: *Characteristic Physical data of* **7c–h** *(cis) and* **8c–H** *(trans) esters prepared by the methods A–D*

Products	Mp [°C] (Solvent)	Molecular Formula (Mw.)	a, IR(KBr), [cm^{-1}] indole NH, ester CO	^{1}H-NMR($CDCl_3$) δ (ppm) = indole NH, 12b-H; 1-CH_2-CH_3	Methods Yields [%] A	B	C	D
7c	140–141 (MeOH)	$C_{21}H_{28}N_2O_2$ (340.45)	3400; 1732	7.79, 3.32, 1.15	51	81	–	–
8c	150–152 (MeOH)	$C_{21}H_{28}N_2O_2$ (340.45)	3320; 1708	8.85, 3.33, 0.67	20	7	–	–
7d	136–138 (EtOH)	$C_{22}H_{30}N_2O_2$ (354.48)	3480; 1738	7.85, 3.28, 1.04	56	78	–	–
8d	105–107 (EtOH)	$C_{22}H_{30}N_2O_2$ (354.48)	3390; 1725	8.90, 3.30, 0.65	22	10	–	–
7e	166–168 (i-PrOH)	$C_{23}H_{32}N_2O_2$ (368.5)	3400; 1720	7.86, 3.32, 1.11	–	–	58	53
8e	96–98 (i-PrOH)	$C_{23}H_{32}N_2O_2$ (368.5)	3380; 1710	8.86, 3.33, 0.67	–	–	63	47
7f	117–118 (CH_3CN)	$C_{24}H_{34}N_2O_2$ (382.53)	3420; 1720	7.86, 3.30, 1.10	58	70	–	–
8f	104–105 (CH_3CN)	$C_{24}H_{34}N_2O_2$ (382.53)	3320; 1705	8.91, 3.33, 0.67	12	8	–	–
7g	146–147 (CH_3CN)	$C_{24}H_{34}N_2O_2$ (382.53)	3380; 1705	7.86, 3.32, 0.81	60	–	65	51
8g	99–101 (i-PrOH)	$C_{24}H_{34}N_2O_2$ (382.53)	3320; 1700	8.98, 3.35, 0.68	11	–	69	48
7h	193–194 (i-BuOH)	$C_{24}H_{34}N_2O_2$ (382.53)	3380; 1710	7.85, 3.33, 1.13	70	78	–	72
8h	121–122 (i-PrOH)	$C_{24}H_{34}N_2O_2$ (382.53)	3320; 1695	9.15, 3.33, 0.70	6	6	–	60

a, Satisfactory microanalyses obtained: C ± 0.30, H ± 0.30, N ± 0.30

The mixture of the epimers **7c–h** and **8c–h** obtained by hydrogenation and richer in the *cis* isomer was separated by crystallization and preparative layer chromatography. The structures were determined, based on data from literature[2e], by ^{1}H-NMR spectroscopy. In the spectra of the *trans* isomer **8** the proton of the indole NH group appears downfield and the methyl protons of the ethyl group upfield with respect to the signals of the *cis* isomers **7**.

If the *trans* compounds of type **8** are to be prepared in larger quantities, it is advantageous to reduce the iminium salts **6c–h** with $NaBH_4$, yielding epimers **7c–h** and **8c–h** in nearly equal amounts. The mixture of epimers **7c** and **8c**, obtained by $NaBH_4$, reduction of iminium salt **6c**, is hydrolyzed with aqueous ethanolic KOH to yield the carboxylic acids **7i** and **8i**, which are easy to separate on the basis of different solubilities in DMF.

From the carboxylic acids **7i** and **8i** the esters **7e,g** or **8e,g**, resp., can also be prepared by alkylation with the corresponding alkyl bromide in HMPA in the presence of anhydrous K_2CO_3 (Method C).

From acid chlorides **9a,b**, obtainable from the carboxylic acids **7i** and **8i** with thionyl chloride, the esters **7e,g,h** or **8e,g,h**, could be prepared with the appropriate alcohol without purification of the sensitive acid chlorids (Method D).

For the synthesis of (+)-vincamine **(1a)** and its derivatives, only the 1(*S*), 12b(*S*) enantiomer of the *cis* ester **7b** can be used. A very simple method was elaborated by means of which the removal of the *trans* epimer **8c** and the separation of the enantiomers of racemic **7c** can be gained in one step. By treating a methylene chloride solution of the mixture of the epimers **7c** and **8c** obtained in the hydrogenation of the iminium salt **6c** in DMF in the presence of Pd-C with (−)-D-dibenzoyltartaric acid, the salt of the (−)-1(*S*), 12b(*S*) enantiomer (−)-**7c** can be obtained free of the other epimer, in full optical purity. From the mother liquor the (+)-1(*R*), 12b(*R*) enantiomer (+)-**7c** and the racemic *trans* ester **8c** could also be isolated in pure form. A further advantage of this method is the possibility to racemice the (+)-1(*R*), 12b(*R*) enantiomer by $Na_2Cr_2O_7$ oxidation ("chromic effect")[7]. Thus both, the (+)-**7c** ester and the racemic *trans* epimer **8c**, can be reconverted into the racemic iminium salt **6c**.

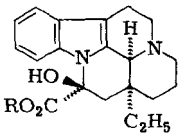
From the enantiomers (−)-**7c** and (+)-**7c** the optically active acids can also be prepared, which yield the desired optically active esters by means of the methods described.

Racemic esters **7c–h** and **8c–h** and some of their enantiomers have strong haemodynamic effects. The *cis* isomers **7c–h** accelerate primarily the cerebral flow, while the *trans* isomers **8c–h** affect extremital circulation. According to the investigations, the vasodilating effect of these compounds significantly surpasses that of (+)-vincamine[8].

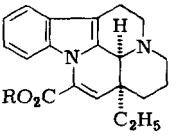
The lactam (+)-**10**[2c], important in view of the synthesis of (+)-vincamine and (+)-apovincaminic esters, was obtained by boiling a toluene solution of methyl ester (−)-**7c** in the presence of a NaH suspension. We have found that the lactam (+)-**10** can also be prepared by the intramolecular acylation[9] of (+)-**7i** carboxylic acid at room temp. upon effect of phosphoryl chloride. The carboxylic acid can be prepared from the ester (−)-**7c** by alkaline hydrolysis. The yield of lactam is 77 % calc. for the ester.

The α-isonitrosation of the lactam (+)-**10** leads to the formation of a *Z,E* isomeric mixture of lactam oxime (+)-**11**[2c,g,10], which, according to the literature, contains the *Z* isomer in about four-fold quantity[10]. Our investigation indicated that under the conditions applied the *E*-oxime is formed in a larger quantity, which could be isolated from the mixture by salt formation and crystallization, too.

There are several methods in the literature for the transformation of (+)-**11** oxime into the α-oxolactam (+)-**12** or (+)-vincamine[2c,g]. We found that the oxime (+)-**11** can be transformed into the α-oxolactam (+)-**12** with a yield of 60.7 % by boiling in glacial acetic

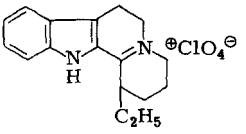


1



2

1, 2	R
a	CH_3
b	C_2H_5



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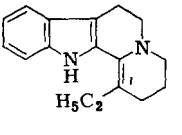

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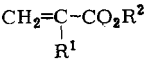

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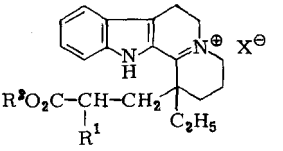

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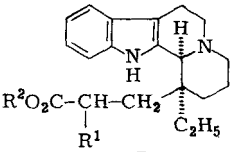

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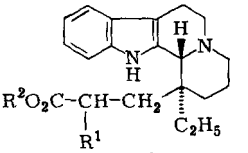
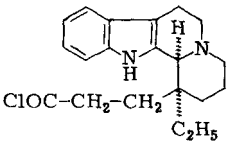


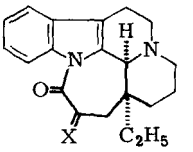
8

5-8	R^1	R^2		R^1	R^2
a	$OCOCH_3$	$-CH_3$	f	H	$-CH_2CH(CH_3)_2$
b	OH	$-CH_3$	g	H	$-CH(C_2H_5)(CH_3)$
c	H	$-CH_3$	h	H	$-C(CH_3)_3$
d	H	$-C_2H_5$	i	H	H
e	H	$-CH(CH_3)_2$			



9

9	12b-H
a	α
b	β



	X
10	H_2
11	N–OH
12	O

acid in the presence of p-toluenesulfonic acid and paraformaldehyde, from which (+)-vincamine **(1a)** can be prepared by base catalyzed methanolysis and epimerization[2c]. The conversion of the oxime (+)-**11** into (+)-vincamine can also be performed without purification of the intermediate oxolactam in a yield of 42%.

When it became known that there are derivatives with significant therapeutical value among the apovincaminic esters, attempts were made to synthesize these compounds directly from the lactam oxime (+)-**11**. When this oxime was heated in methanol or ethanol in the presence of concentrated sulfuric acid, (+)-apovincamine **2a** or (+)-apovincaminic ethyl ester **2b**, could be isolated in yields of ca. 70–80%.

The enantiomeric purity of (+)-**2b** was determined by ^{1}H-NMR spectroscopy. In the presence of Eu-optishift-reagent the olefinic proton of (+)-**2b** (δ = 6.10 ppm) gave a singlet, which splits into double signals in the case of rac.-**2b**.

(+)-Apovincaminic ethyl ester **(2b)** is a pharmacon registered under the name CAVINTON® and widely used in the therapy. As excellent cerebral vasodilator, it is successfully applied in the therapy of cerebral circulation disorders and of ophthalmologic and auditory problems[3].

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Experimental

IR spectra: Spectromom spectrophotometer. *^{1}H-NMR spectra*: Varian XL-100-15-124XL 16K Fourier transform and JEOL JNM-FX-100 multinuclear spectrometers, chemical shifts δ = ppm downfield from TMS. *Mass spectra*: JEOL-01 SG-2 instrument (70 eV, ion source temp. 150°, direct insertion). *M.p.*: uncorr.

General method for the preparation of the perchlorates **6c–h**

The suspension of 3.00 g, (8.52 mmole) perchlorate **3** in 60 ml methylene chloride was stirred with 55 ml 2% NaOH solution for 10 min. The organic layer was separated, dried (K_2CO_3) and to the filtrate 33.2 mmole of the corresponding acrylic esters **5c–h**, was added and the mixture was allowed to stand at room temp. for 2 d. The solvent was removed i.vac. and the residual red oil was dissolved in the corresponding alcohol and acidified with 70% $HClO_4$ to pH 5. The yellow perchlorates were recrystallized (Table 1.).

General methods for the preparation of alkyl-3-(1α-ethyl-1,2,3,4,6,7,12,12bα- **7c–h** and *12bβ-octahydro-indolo[2,3-a]quinolizin-1β-yl)-propionates* **8c–h**

Method A: 10.4 mmole of the perchlorates **6c–h** were dissolved in the mixture of 130 ml methanol and 20 ml methylene chloride and hydrogenated over 2.0 g 10% Pd-C at room temp. and atmospheric pressure. When the reduction was complete (2 h), the suspension was filtered to remove the catalyst and the solvent was evaporated at reduced pressure. The residue was dissolved in 20 ml methylene chloride and partitioned against a 5% Na_2CO_3 solution. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness i.vac. to give a mixture of the epimers **7c–h** and **8c–h**, which were separated by preparative TLC (silica gel, benzene-methanol 14:3, elution with CH_2Cl_2-CH_3OH 10:2, Rf: **7c–h** > **8c–h**) (Table 2.).

Method B: 10.4 mmole of the perchlorates **6c–h** were dissolved in 15 ml DMF and hydrogenated over 2.0 g 10 % Pd-C. When the reduction was complete (1 h), the catalyst was removed. To the filtrate 30 ml water was added, the solution was basified with 30 % NH_4OH to pH9 and the precipitate was washed with water and dried. The crude products were recrystallized from the corresponding alcohols to give the *cis* compounds **7c–h**. The alcoholic mother liquors were purified by TLC following method A (Table 2.).

Method C: The solution of carboxylic acids **7i** or **8i** (1.63 g, 4.99 mmole) in 12.5 ml HMPA was stirred with 0.80 g of finely powdered K_2CO_3 and 22.0 mmole of the corresponding alkylbromide at room temp. for 24 h. The reaction mixture was poured into 100 ml ice water and extracted with 3 × 30 ml ether. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was recrystallized from the corresponding alcohol (Table 2.).

Method D: 2.00 g (6.12 mmole) of the carboxylic acids **7i** or **8i** were added in portions to 6 ml thionyl chloride at 0 °C under stirring. The stirring was continued for 1 h, thereafter the hydrochlorides were precipitated with 30 ml anhydrous ether. The solvent was decanted and the residual crystalline products were washed several times with ether to remove traces of the reagent. The hydrochlorides of acid chlorides were then dissolved in 15 ml of the corresponding alcohol and stirred at 0 °C for 1 h. The solvent was evaporated under reduced pressure, the residue was then dissolved in water, basified with conc. NH_4OH solution and extracted with methylene chloride. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue was crystallized from the corresponding solvent (Table 2.).

3-(1α-Ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-a]quinolizin-1β-yl)-propionic acid (**7i**) and *3-(1α-ethyl-1,2,3,4,6,12,12bβ-octahydro-indolo[2,3-a]quinolizin-1β-yl)-propionic acid* (**8i**)

To a stirred suspension of 8.29 g (18.9 mmole) iminium perchlorate **6c** in 80 ml methanol 0.70 g sodium borohydride was added in portions at 0 °C. After the addition was complete, stirring was continued for 30 min, the mixture acidified with glacial acetic acid to pH 6, and evaporated to dryness i.vac. The residue was treated with 5 % Na_2CO_3 solution and extracted with methylene chloride. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residual oil (6.00 g, 93 %) was dissolved in 95 % ethanol and 1.5 g NaOH was added to the solution and boiled for 1 h; the solvent was removed i.vac., the residue was dissolved in 30 ml water, the solution acidified with acetic acid to pH 6 and the precipitated mixture of epimeric acids **7i** and **8i** washed with water and dried (5.40 g, 94 %). The epimeric mixture was recrystallized from 36.5 ml DMF to yield the *trans* acid **8i** (2.56 g, 47.5 %). M.p. 148–150 °C. IR (KBr): 3200 (broad, indole NH, OH), 1650 and 1550 cm^{-1} (COOH). $C_{20}H_{26}N_2O_2$ (326.43). Calc.: C 73.6 H 8.02 N 8.6; Found: C 73.4 H 8.11 N 8.5.

The DMF mother liquor was diluted with 8.1 ml water. The crystalline product was washed with a mixture of DMF and water 5 : 1 and then with water to yield 1.89 g of the *cis* acid **7i** (35 %). M.p. 249–250 °C. IR (KBr): 3150 (broad, indole NH, OH), 1650 and 1560 cm^{-1} (COOH). $C_{20}H_{26}N_2O_2$ (326.43). Calc.: C 73.6 H 8.02 N 8.6; Found: C 73.3 H 8.25 N 8.4.

*(−)-1(S), 12b(S)-***7c**, *(+)-1(R),12b(R)-***7c** *enantiomers and rac.-***8c** *ester*

A solution of 27.50 g (62.65 mmole) **6c** perchlorate in 140 ml DMF was hydrogenated over 10 g 10 % Pd-C at room temp. under normal pressure. When the hydrogen consumption had ceased (1.5 h), the catalyst was removed and washed with 2 × 10 ml DMF. The filtrate was diluted with 300 ml water and basified with conc. NH_4OH solution to pH 9. The precipitate was washed with water and dried to yield a mixture of **7c** and **8c** (24.5 g, 97 %). This mixture was dissolved in 80 ml methylene chloride and a solution of 25.0 g D-dibenzoyl-tartaric acid in 160 ml methylene chloride was added. Then the solution

was boiled for 2–3 min and allowed to stand at room temp. for 2 h. The precipitated crystals were washed with methylene chloride (mother liquor A) to yield D-dibenzoyl-tartaric acid salt of (−)-**7c** (20.0 g, 40 %). M.p. 152 °C; $[\alpha]_D^{20} = -90.4°$ (DMF, c = 2.02). A suspension of this salt in 50 ml methylene chloride was extracted with 3 × 50 ml 5 % Na_2CO_3 solution. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness to give (−)-**7c** methylester as a colourless oil (9.80 g, 40 %). $[\alpha]_D^{22} = -121°$ (CH_2Cl_2, c = 2.02). The hydrochloride of (−)-**7c** melted at 254 °C (methanol).

The methylene chloride mother liquor A (~250 ml) was extracted with 3 × 50 ml 5 % Na_2CO_3 solution. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to dryness. Recrystallization of the residue (13.40 g) from 30 ml methanol gave rac. **−8c** (2.0 g, 8.1 %), m.p. 150 °C (Lit.[2c] m.p. 149 °C).

The methanolic filtrate was acidified with HCl-MeOH to pH 5 and the white hydrochloride of (+)-**7c** was separated (6.00 g, 23 %), m.p. 257 °C (methanol). The (+)-**7c** base was deliberated from the hydrochloride with 5 % Na_2CO_3 solution. $[\alpha]_D^{22} = +126°$ (CH_2Cl_2, c = 1.54).

*(+)-14-Oxo-E-homo-eburnane [(+)-**10**]*

A. A solution of 9.80 g (28.8 mmole) (−)-**7c** methylester in 450 ml dry toluene was heated to reflux with a 50 % suspension of 1.80 g sodium hydride under stirring for 5 h and then allowed to cool to 22 °C. The solution was extracted with 3 × 120 ml 2.5 % aqueous sulfuric acid. The combined acidic layer was treated with conc. NH_4OH solution to pH 9 and extracted with 3 × 60 ml methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The residue was recrystallized from methanol to yield 5.30 g of (+)-**10** (60 %). M.p. 155–157 °C; Lit.[2g] m.p. 154–155 °C. IR (KBr): 1700 cm^{-1} (lactam CO). MS m/e (%): 308 (M^+, 100), 307 (53), 280 (14), 279 (14), 252 (22). $[\alpha]_{546}^{22} = +29.5°$ (DMF, c = 1.00). rac. -**10**, m.p. 165–167 °C (methanol).

B. A solution of 20.00 g (58.82 mmole) (−)-**7c** methylester in 190 ml 95 % ethanol was boiled with 10.0 g NaOH for 1.5 h. The solvent was removed i. vac., the residue was dissolved in 120 ml ice-water, the solution acidified with acetic acid to pH 6 and extracted with 3 × 40 ml chloroform. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to yield (+)-**7i** acid (18.23 g, 95 %). M.p. 136–140 °C. $[\alpha]_D^{22} = +116°$ (DMF, c = 0.60). 18.23 g of the acid (+)-**7i** was dissolved in 200 ml phosphoryl chloride and stirred at room temp. for 24 h. The reaction mixture was then diluted with 200 ml anhydrous benzene and evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml methylene chloride, 50 ml ice-water was added to the solution and the pH was adjusted to 9 with conc. NH_4OH. The organic layer was evaporated, dried ($MgSO_4$) filtered and evaporated to dryness. The residual oil (18.70 g) was recrystallized from methanol to yield (+)-**10** lactam (13.96 g, 77 %), which was in all respects identical with that prepared according to A.

*(+)-14-Oxo-15-hydroxyimino-E-homo-eburnane [(+)-**11**]*

To a suspension of 2.10 g (6.8 mmole) (+)-**10** lactam in 24 ml dry toluene, 4.8 ml tert. butyl nitrite and 1.53 g (13.1 mmole) t. BuOK were added. The reaction mixture was stirred under nitrogen at room temp. for 1 h. A solution of 4.2 g NH_4Cl in 80 ml water was added and stirring was continued for 15 min. The organic layer was separated and the aqueous phase was extracted with 3 × 10 ml methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The residual mixture of *Z* and *E* oximes (1.90 g) was dissolved in 6 ml methanol, acidified with HCl-CH_3OH to pH 4. The crystalline product was washed with methanol to yield (+)-**11** *E*-oxime hydrochloride (1.60 g, 63 %). M.p. 256–257 °C; Lit.[10] m.p. 230–240 °C. The free

base was deliberated with 5 % Na_2CO_3 solution and recrystallized from ether. M.p. 195 °C; Lit.[10] m.p. 201 °C. IR (KBr): 3200 (OH), 1705 (lactam CO), 1640 cm^{-1} (C=N). $C_{20}H_{23}N_3O_2$ (337.40) Calc.: C 71.2 H 6.87 N 12.5; Found: C 71.2 H 6.68 N 12.5. $[\alpha]_D^{22}$ = +62° (Pyridine, c = 1.00); Lit.[10] $[\alpha]_D$ = +62° (Pyridine, c = 1.00). rac. **-11**, m.p. 258 °C (toluene).

*(+)-14,15-Dioxo-E-homo-eburnane [(+)-**12**]*

A solution of 0.50 g, (1.48 mmole) (+)-**11** oxime in 10 ml glacial acetic acid was refluxed with 0.50 g dry p-TsOH and 0.50 g paraformaldehyde for 5 h under stirring. After cooling, the reaction mixture was poured into 50 ml ice-water, treated with conc. NH_4OH solution to pH 9 and extracted with 3 × 30 ml methylene chloride. The combined organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residual oil was crystallized from ether to yield (+)-**12** (0.29 g, 60.7 %). M.p. 117 °C; Lit.[2c] m.p. 116–117 °C. IR (KBr): 1730 (CO), 1695 cm^{-1} (lactam CO). MS m/e (%): 322 (M^+, 100), 294 (86), 266 (80), 252 (88), 237 (41), 197 (42), 169 (40), 168 (40). $[\alpha]_D^{22}$ = +80.3 ($CHCl_3$, c = 0.90). rac. **-12**, m.p. 156° (ether).

*(+)-Vincamine [(+)-**1**]*

A solution of 0.27 g (0.80 mmole) (+)-**11** oxime in 6 ml glacial acetic acid was heated at 103–105 °C with 0.27 g p-TsOH and 0.27 g paraformaldehyde for 5 h under stirring. The cold solution was poured into 20 ml ice-water, treated with conc. NH_4OH to pH9 and extracted with 3 × 10 ml methylene chloride. The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in 1.2 ml methanol containing 30 mg of t-BuOK and the reaction mixture was allowed to stand at room temp. for 2 h. The crystals were washed with cold methanol to give 0.12 g (42 %) of (+)-vincamine, identical with authentic sample. M.p. 234–235 °C, $[\alpha]_D^{22}$ = +45° (Pyridine, c = 0.89).

(+)-Apovincamine (**2a**)

2.00 g (5.93 mmole) of the (+)-**11** oxime was heated in the mixture of 44 ml methanol and 16 ml conc. sulfuric acid on a water bath for 2.5 h. The cold solution was poured into 100 ml ice-water, basified with conc. NH_4OH solution to pH 9 and extracted with 3 × 40 ml methylene chloride. The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness i.vac. The residue was recrystallized from methanol to yield 1.30 g (65 %) of **2a**. M.p. 160–162 °C; Lit.[11] m.p. 160–162 °C. $[\alpha]_{546}^{26}$ = +170° ($CHCl_3$, c = 0.978); Lit.[11] $[\alpha]_{546}^{25}$ = +172° ($CHCl_3$, c = 0.978). MS m/e (%): 336 (M^+, 43.8), 307 (100), 266 (87.2), 207 (25). IR (KBr): 1735 (ester CO), 1635 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.20–7.00 (4H, m, aromatic), 6.10 (1H, s, olefinic H), 4.10 (1H, 3-H), 3.90 (3H, s, CO_2CH_3), 1.02 ppm (3H, t, J = 7.3 cps, $CH_2\underline{CH_3}$). rac. **-2a**, m.p. 133–135 °C (methanol).

*(+)-Apovincaminic acid ethylester, Cavinton® [(+)-**2b**]*

0.27 g (0.8 mmole) of the (+)-**11** oxime was heated in a mixture of 5.5 ml ethanol and 1.95 ml conc. sulfuric acid on a water bath for 5 h. The cold solution was poured into 20 ml ice-water, basified with conc. NH_4OH to pH 9 and extracted with 4 × 10 ml methylene chloride. The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The residual oil was recrystallized from 1 ml ethanol to yield 0.19 g (67.6 %) of (+)-**2b**, identical in every respects with the authentic sample[3a]. M.p. 149–152 °C. MS m/e (%): 350 (54.8), 321 (100), 292 (6.6), 280 (73.9), 206 (7). IR (KBr): 1740 (ester CO), 1640 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.48–7.0 (4H, m, aromatic), 6.10 (1H, s, olefinic H), 4.42 (2H, q, J = 7.3 cps, $CO_2\underline{CH_2}CH_3$), 4.15 (1H, 3-H), 1.40 (3H, t, J = 7.3 cps, $CO_2CH_2\underline{CH_3}$), 1.00 ppm (3H, t, J = 7.3 cps, $CH_2\underline{CH_3}$). $[\alpha]_D^{22}$ = +147° ($CHCl_3$, c = 1.10). rac. **-2b**, m.p. 122 °C (ethanol).

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Synthesis of 2-Substituted Thiobenzimidazoles as Potential Anthelminthics[1)]

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The 2-substituted thiobenzimidazoles **7–19** have been synthesized and tested for their anthelminthic activity against *Ancylostoma ceylanium* and *Hymenolepsis nana* in hamsters and rats, respectively.

Synthese 2-substituierter Thiobenzimidazole als potentielle Anthelminthica

Die 2-substituierten Thiobenzimidazole **7–19** wurden synthetisiert und auf ihre anthelminthische Aktivität gegen *Ancylostoma ceylanium* und *Hymenolepsis nana* an Hamster und Ratte getestet.

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