Synthesis of Vinca Alkaloids and Related Compounds, XLIV[1]:

Synthesis of Trifluoro-apovincaminic Acid Ester

Mària Incze, Ferenc Sóti, Zsuzsanna Kardos-Balogh, Mária Kajtár-Peredy, and Csaba Szántay

Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest II. Pusztaszeri ut 59-67, H-1525, Hungary

Received May 8, 1989

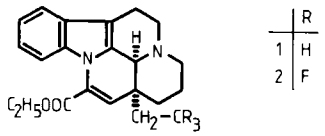
Via the intermediate iminium salt **8** the 21,21,21-trifluoro-apovincaminic acid ethyl ester (**2**), a derivative of CAVINTON^R (**1**) was synthesized. The pharmacological effect of **2** changed dramatically compared with the parent compound.

Über die Synthese von Vinca-Alkaloiden und verwandten Verbindungen, 44. Mitt.[1]:
Synthese von Trifluorapovincaminsäure Ethylester

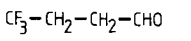
Über das Zwischenprodukt des Iminium Salzes **8** wurde der 21,21,21-Trifluor-apovincaminsäure Ethylester (**2**), ein Derivat von CAVINTON^R (**1**) synthetisiert. Der pharmakologische Effekt von **2** veränderte sich dramatisch im Vergleich mit dem der ursprünglichen Verbindung.

The ethyl ester of (+)-apovincaminic acid (CAVINTON^R, **1**) is an effective cerebral vasodilator[2]. In search for more information about the structure-activity relationship we aimed at the synthesis of the trifluoro derivative **2**.

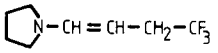
At the outset the most practical approach seemed to be a simple alkylation of malonic acid ethyl ester with 2,2,2-trifluoroethyl halide and using the product according to our previously described reaction sequence[3]. However, due to the diminished reactivity of trifluoroethyl halides[5,6] in spite of all of our efforts, such an alkylation could not be carried out in detectable yields. Although the 2,2,2-trifluoroethyl malonic acid ethyl ester is a known compound[4], its synthesis using an electrochemical method is rather tedious. Therefore, we had to change our original strategy to follow a different reaction sequence.



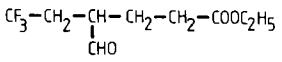
	R
1	H
2	F



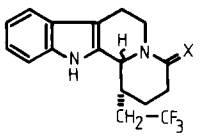
3



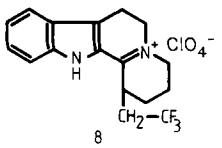
4



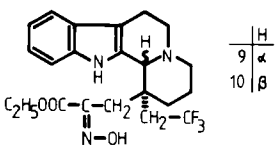
5



	H	X
6a	α	O
6b	β	O
7a	α	H_2
7b	β	H_2



8



	H
9	α
10	β

The enamine **4**, obtained from 4,4,4-trifluoro-butyraldehyde (**3**)[8] and pyrrolidine, was reacted with ethyl acrylate. Unlike the corresponding enamine derived from butyraldehyde[7], **4** reacted only with one equivalent of acrylic ester. After hydrolysis the isolated ester aldehyde **5** was reacted with tryptamine resulting in lactam **6**. On subsequent reduction with $LiAlH_4$, and oxidation with Hg(II) acetate, the iminium salt **8** was obtained. The enamine derived from the salt **8** was reacted with the oxime of bromopyruvic acid ethyl ester. A similar reaction was mentioned by *Wenkert*[9] in a footnote, and we have used it with advantage in our synthesis of de-ethyl vincamine[10].

The reaction of the enamine with the bromo-oxime derivative was followed by catalytic reduction yielding both the *cis* (**9**) and *trans* (**10**) epimers. Boiling of the *cis* isomer with acid in ethanol gave the end-product **2**.

Comparative pharmacological investigations of **2** and CAVINTON^R (**1**) revealed the almost complete lack of any useful activity of **2**. This somewhat surprising result shows the significance of the C-16-ethyl group in **1** seemingly being an important site of the biological effect. To throw some light on the biological role of the C-16-substituent is the aim of our further studies.

The authors wish to thank *J. Tamás* for mass spectra, *G. Keresztury* for IR spectra, the Hungarian Academy of Sciences and the Gedeon Richter Pharmaceutical Company (Budapest) for financial support.

Experimental Part

Infrared spectra: Nicolet 7199 Fourier transform spectrometer, frequencies (cm^{-1}) of significant peaks are reported.- ^1H- and ^{13}C-NMR spectra: 100 and 25 MHz, respectively; Varian XL-100 FT, $CDCl_3$, chemical shifts in ppm relative to internal TMS.- Mass spectra: AEI-902 mass spectrometer (70 eV, ion source temp. 200°C, direct insertion).- Purification of

  0365-6233/90/0606-0331 $ 02.50/0

the compounds was carried out by column chromatography on silica gel (Merck Kieselgel 60, 0.063-0.2 mm).

1-Pyrrolidyl-4,4,4-trifluoro-1-butene (**4**)

4,4,4-Trifluorobutyraldehyde (**3**) (5.4 g, 42.8 mmole) was added at 0°C dropwise to the stirred mixture of pyrrolidine (6.89 g, 97 mmole) and anhydrous K_2CO_3 (2.42 g, 17.5 mmole). The mixture was allowed to stand overnight at room temp. K_2CO_3 was removed by filtration and the filtrate yields **4** (4.99 g, 65%, b.p. 76-8°C/23 mm Hg).- ^{1}H-NMR: δ (ppm) = 1.86 (4H, t, J = 6.6 Hz, N-CH_2-$C\underline{H}_2$-CH_2), 2.70 (2H, qdd, $J_{H,F}$ = 10.8 Hz, J_{vic} = 7.4 Hz, J_{allyl} = 0.8 Hz, =CH-$C\underline{H}_2CF_3$), 3.05 (4H, t, J = 6.6 Hz, CH_2-N-CH_2), 3.92 (1H, dt, J_{trans} = 13.4 Hz, J_{vic} = 7.4 Hz, -CH=C$\underline{H}$-CH_2), 6.32 (1H, d, J_{trans} = 13.4 Hz, N-CH=).

Ethyl 4-formyl-6,6,6-trifluorocaproate (**5**)

Ethyl acrylate (6.89 g, 69 mmole) was dissolved in dry ethanol (23.5 ml) with stirring under argon. The solution was cooled to 0°C and **4** (4.9 g, 27 mmole) was added dropwise. The mixture was stirred for 5 h at room temp., then refluxed for 2 h. Acetic acid (2.6 ml) and water (14.3 ml) was added to the mixture and refluxed for an additional 8 h. The solvent was evaporated, the residue diluted with water (35 ml) and extracted with methylene chloride. The dried ($MgSO_4$) org. phase was evaporated and the residue distilled to yield **5** (3.4 g, 55%, b.p. 50°C/0.25 mm Hg).- ^{1}H-NMR: δ (ppm) = 1.26 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.8-3.0 (7H, m, -CH_2-C$\underline{H}$-$(CH_2)_2$-), 4.16 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 9.69 (1H, broad s, -CHO).- ^{13}C-NMR: δ (ppm) = 14.17 ($OCH_2\underline{C}H_3$), 23.80 (CH-$\underline{C}H_2$-CH_2), 30.85 ($\underline{C}H_2CO$), 32.19 ($^2J_{C,F}$ = 29.3 Hz, $\underline{C}H_2CF_3$), 44.89 ($^3J_{C,F}$ = 2.0 Hz, CH), 60.84 ($O\underline{C}H_2CH_3$), 126.42 ($^1J_{C,F}$ = 276.7 Hz, CF_3), 172.31 ($\underline{C}OOEt$), 200.16 ($^4J_{C,F}$ = 0.3 Hz, CHO).

1-(2,2,2-Trifluoroethyl)-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]-quinolizine-4-on (**6**)

Tryptamine (2.4 g, 15 mmole) and **5** (3.4 g, 15 mmole) were refluxed in benzene (30 ml) for 5 h with a water separating equipment. After removal of the solvent in vacuo the residue was dissolved in acetic acid (50 ml) and refluxed for 2 h. The solvent was evaporated and the residue extracted with chloroform. The dried ($MgSO_4$) org. phase was evaporated and the residue, purified by column chromatography on silica gel with elution by 10% v/v diethylamine:toluene, gave **6a** and **6b**. R_f **6a** > **6b**.

6a: 2.1 g (43.3%), m.p. 222-225°C.- MS: m/z (%): 323 (24), 322 (100, M^+), 321 (16), 239 (11, M-83), 212 (24, M-110), 211 (21), 171 (21), 170 (90, M-152), 169 (77), 168 (18).- IR ($CHCl_3$): 3468 (indole NH); 1639 (lactam C=O); 1269; 1255; 1139 (CF_3).- ^{1}H-NMR: δ (ppm) = 1.6-3.3 (10H, m, C(1)H + $C(2)H_2$ + $C(3)H_2$ + $C(6)H_a$ + $C(7)H_2$ + $C\underline{H}_2CF_3$), 4.76 (1H, broad s, C(12b)H), 5.06 (1H, m, $C(6)H_e$), 7.0-7.6 (4H, m, aromat.), 8.32 (1H, broad s, indole NH).- ^{13}C-NMR: δ (ppm) = 20.69 (C-7), 22.28 (C-2), 28.13 (C-3), 28.92 ($^3J_{C,F}$ = 2.1 Hz, Cl), 35.27 ($^2J_{C,F}$ = 27.7 Hz, $\underline{C}H_2CF_3$), 43.50 (C-6), 59.98 (C-12b), 109.98 (C-7a), 111.42 (C-11), 117.88 (C-8), 119.15 (C-9), 121.60 (C-10), 127.02 (C-7b), 127 ($^1J_{C,F}$ = 275 Hz, CF_3), 133.03 (C-12a), 136.34 (C-11a), 169.50 (C-4).

6b: 1.5 g (31%), yellow oil.- MS m/z (%): 323 (21), 322 (100, M^+), 321 (18, M-1), 239 (10, M-83), 212 (24), 211 (21), 171 (20), 170 (94, M-152), 169 (75), 168 (14).- IR ($CHCl_3$): 3466 (indole NH); 1636 (lactam C=O); 1268; 1255; 1146 (CF_3).- ^{1}H-NMR: δ (ppm) = 1.5-3.0 (10H, m, C(1)H + $C(2)H_2$ + $C(3)H_2$ + $C(6)H_a$ + $C(7)H_2$ + CH_2CF_3), 4.99 (1H, broad s, C(12b)H), 5.17 (1H, m, $C(6)H_e$), 7.0-7.6 (4H, m, aromat.), 8.22 (1H, broad s, indole NH).- ^{13}C-NMR: δ (ppm) = 20.79 (C-7), 22.66 (C-2), 27.55 (C-3), 30.78 ($^3J_{C,F}$ = 2.1 Hz, C-1), 28.97 ($^2J_{C,F}$ = 27.7 Hz, $\underline{C}H_2CF_3$), 39.29 (C-6), 57.82 (C-12b), 110.54 (C-7a), 111.34 (C-11), 118.07 (C-8), 119.14 (C-9), 121.76 (C-10), 126.37 (C-7b), 127.8 ($^1J_{C,F}$ = 275 Hz, CF_3), 130.69 (C-12a), 137.00 (C-11a), 168.88 (C-4).

1-(2,2,2-Trifluoroethyl)-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]-quinolizine (**7**)

To a stirred suspension of $LiAlH_4$ (6 g) in dry THF (100 ml) a mixture of **6a** and **6b** (7.3 g, 22.6 mmole) dissolved in dry THF (200 ml) was added dropwise. The mixture was refluxed for 2 h. The excess hydride was decomposed with water. The org. layer was decanted, dried over Na_2SO_4 and evaporated to supply a mixture of **7a** and **7b**, combined yield 4.5 g (64.4%), which were separated by column chromatography for NMR analysis.

^{1}H-NMR of **7a**: δ (ppm) = 1.4-1.7 (4H, m), 2.3-3.4 (9H, m), 4.04 (1H, broad s, C(12b)H), 6.95-7.55 (4H, m, aromat.), 7.90 (1H, broad s, indole NH).- ^{13}C-NMR: δ (ppm) = 18.06 (C-7), 20.26 (C-3), 30.18 ($^3J_{C,F}$ = 2.1 Hz, C-1), 30.32 (C-2), 36.23 ($^2J_{C,F}$ = 27.3 Hz, $\underline{C}H_2CF_3$), 47.35 (C-4), 50.61 (C-6), 58.84 ($^4J_{C,F}$ = 0.7 Hz, C-12b), 108.59 (C-7a), 111.03 (C-11), 118.12 (C-8), 119.51 (C-9), 121.61 (C-10), 127.54 ($^1J_{C,F}$ = 277.2 Hz, CF_3), 127.62 (C-7b), 132.47 (C-12a), 135.86 (C-11a).

^{1}H-NMR of **7b**: δ (ppm) = 1.5-3.1 (13H, m, C(1)H + $C(2)H_2$ + $C(3)H_2$ + $C(4)H_2$ + $C(6)H_2$ + $C(7)H_2$ + CH_2CF_3), 3.44 (1H, broad s, C(12b)H), 6.95-7.55 (4H, m, aromat.), 7.68 (1H, broad s, indole NH).

1-(2,2,2-Trifluoroethyl)-1,2,3,4,6,7-hexahydro-12H-indolo-[2,3-a]-quinolizinium perchlorate (**8**)

To a stirred solution of **7a** and **7b** (2.1 g, 6.8 mmole) in acetic acid (100 ml) a solution of Hg(II) acetate (2.1 g, 21.9 mmole) in acetic acid (100 ml) was added. The mixture was kept at 60°C for 6 h. After cooling the solution was basified with conc. NH_4OH solution to pH 10 and extracted with methylene chloride (5x20 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in ethanol (10 ml) and acidified with 70% $HClO_4$ to pH 3 to give yellow crystals of **8** (1.78 g, 64%, m.p. 227-229°C).- MS m/z (%): 307 (14), 306 (69, M^+), 305 (17, M-1), 238 (19), 237 (100, M-69), 223 (28, M-83).- IR (KBr): 3400 (indole NH); 1626 (C=C, B/C rings); 1547 ($C=N^+$); 1277; 1263 and 1148 (CF_3); 1095 and 624 (ClO_4^-).- ^{1}H-NMR ($CDCl_3$ + DMSO-d_6): δ (ppm) = 1.9-3.5 (9H, m, C(1)H + $C(2)H_2$ + $C(3)H_2$ + $C(7)H_2$ + CH_2CF_3), 3.8-4.4 (4H, m, $C(4)H_2$ + $C(6)H_2$), 7.1-7.7 (4H, m, aromat.), 11.55 (1H, broad s, indole NH).

Ethyl 3-[1α-(2,2,2-trifluoroethyl)-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-a]quinolizin-1β-yl)-2-hydroxyiminopropionate (**9**)

The salt **8** (1.2 g, 2.9 mmole) was dissolved in methylene chloride (10 ml) and treated with 2% NaOH (10 ml). After separation the org. layer was dried ($MgSO_4$) and evaporated. To the stirred solution of the enamine in methylene chloride (10 ml) aq. NaOH (10%, 1.3 ml) and solution of the oxime of ethyl bromopyruvate (0.67 g, 3.2 mmole) in methylene chloride (1.3 ml) were added simultaneously at -5°C. After separation and evaporation the residue was dissolved in DMF (5 ml) and hydrogenated over 10% Pd-C (0.2 g). When the reduction was complete, the catalyst was removed, the solvent evaporated and the residue recrystallized from acetone to yield **9** as colorless crystals (0.49 g, 61%, m.p. 194-196°C). MS m/z (%): 438 (24), 437 (100, M^+), 436 (43, M-1), 421 (14), 420 (27, M-17), 364 (22, M-73), 348 (11, M-89), 346 (20, M-91), 321 (42, M-116), 307 (32, M-130), 197 (66), 184 (32), 171 (26), 170 (76), 169 (59), 168 (15), 57 (40), 43 (97).- IR (KBr): 3443 (indole NH); 2580 (broad, oxime OH, chelation); 1726 and 1694 (ester C=O); 1291; 1260; 1160 (CF_3 and C-O-C); 1024 (oxime N-O).- ^{1}H-NMR ($CDCl_3$ + DMSO-d_6): δ (ppm) = 1.20 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.4-2.0 (4H, m, $C(2)H_2$ + $C(3)H_2$), 2.2-3.4 (10H, m, $C(4)H_2$ + $C(6)H_2$ + $C(7)H_2$ + CH_2CF_3 + C(1)-CH_2-C=), 3.60 (1H, broad s, C(12b)H), 4.12 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 6.9-7.5 (4H, m, aromat.), 8.53 (1H, broad s, indole NH), 11.6 (1H, broad s, =N-OH).- ^{13}C-NMR ($CDCl_3$ + DMSO-d_6): δ (ppm) = 13.95 ($OCH_2\underline{C}H_3$), 21.83 (C-3), 22.00 (C-7), 27.27 (C-1-$\underline{C}H_2$-C=N), 32.83 (C-2), 41.16 ($^2J_{C,F}$ ≈ 27 Hz, $\underline{C}H_2CF_3$), 68.46 (C-12b), 111.72 (C-11), 112.72 (C-7a), 117.54 (C-8), 118.90 (C-9), 121.24 (C-

10), 126.63 (C-7b), 132.11 (C-12a), 137.09 (C-11a), 150.79 (C=N), 165.02 (COOEt).

The mother liquor, purified by column chromatography on silica gel (10% v/v diethylamine:toluene) gave **10** as a yellow oil (23 mg, 2.9%).- ^{1}H-NMR: δ (ppm) = 1.34 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.3-3.2 (14H, m, $C(2)H_2$ + $C(3)H_2$ + $C(4)H_2$ + $C(6)H_2$ + $C(7)H_2$ + CH_2CF_3 + C(1)-CH_2-C=), 3.35 (1H, broad s, C(12b)H), 4.33 (2H, q, J = 7.0 Hz, OCH_2CH_3), 7.0-7.6 (4H, m, aromat.), 8.55 (1H, broad s, indole NH), 10.13 (1H, broad s, =N-OH).

Ethyl21,21,21-trifluoroapovincaminate (**2**)

A mixture of oxime **9** (0.17 g, 0.39 mmole), ethanol (3 ml) and conc. H_2SO_4 (0.87 ml) was heated for 2 h. The cooled solution was poured into ice-water (20 ml), basified with conc. NH_4OH to pH 9 and extracted with methylene chloride. The org. phase was dried ($MgSO_4$), filtered and evaporated to dryness. The oily residue was recrystallized from ethanol to yield the end-product **2** (0.12 g, 76.4%, m.p. 132-134°C). MS m/z (%): 405 (8), 404 (33, $M^{+\cdot}$), 335 (22), 334 (100, M-70), 321 (29, M-83), 306 (17, M-98), 28 (33).- IR (KBr): 2810, 2730 (Bohlmann bands); 1732 (ester C=O); 1635 (C=C, E ring); 1607 (C=C); B/C rings), 1280; 1261; 1104 (CF_3).- ^{1}H-NMR: δ (ppm) = 1.0-1.8 (4H, m, $C(17)H_2$ + $C(18)H_2$), 1.38 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.3-3.4 (8H, m, $C(19)H_2$ + $C(5)H_2$ + $C(6)H_2$ + CH_2CF_3), 4.15 (1H, broad s, C(3)H), 4.44 (2H, q, J = 7.1 Hz, OCH_2CH_3), 6.34 (1H, q, $^5J_{H,F}$ = 0.8 Hz, C(15)H), 7.05-7.55 (4H, m, aromat.).

References

1 Part XLIII: Zs. Kardos-Balogh, F. Sóti, M. Incze, M. Kajtár-Peredy, L. Radics, and Cs. Szántay, Heterocycles *28*, 303 (1989).
2 Cs. Lörincz, K. Szász, and L. Kisfaludy, Arzneim. Forsch. *26*, 1907 (1976).
3 Cs. Szàntay, L. Szabò, and G. Kalaus, Tetrahedron *33*, 1803 (1977).
4 N. Muller, J. Org. Chem. *51*, 263 (1986).
5 J. Hine and R.G. Ghirardelli, J. Org. Chem. *23*, 1550 (1958).
6 P. Tarrant and J.A. Young, J. Am. Chem. Soc. *75*, 932 (1953).
7 M.E. Kuehne, J. Am. Chem. Soc. *86*, 2946 (1964).
8 H.M. Walborsky, M. Baum, and D.F. Loncrini, J. Am. Chem. Soc. *77*, 3637 (1955).
9 G. Rossey, A. Wick, and E. Wenkert, J. Org. Chem. *47*, 4745 (1982).
10 J. Sápi, L. Szabó, Gy. Kalaus, and Cs. Szántay: in preparation.

[Ph682]