6. (*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid, a Novel Compound from Civet *(Viverra civetta)*

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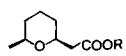
Summary

The isolation and synthesis of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**1a**), a novel compound from civet *(Viverra civetta)*, are reported.

In the course of analysis of the volatile acids of civet[1]) we identified, besides various common aliphatic carboxylic acids (saturated, unsaturated, straight chain and branched, containing 2 to 18 carbon atoms), the heterocyclic carboxylic acid **1a**[2]). To the best of our knowledge, neither the natural occurrence nor the synthesis of this acid has been reported.



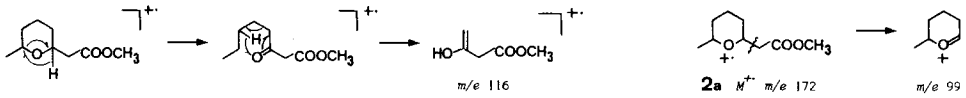
1a R=H
2a R=CH_3

The new compound was isolated and identified in the form of its methyl ester **2a**, the constitution of which was deduced from the spectral data. The mass spectrum (molecular ion at *m/e* 172) and the NMR. spectrum (16 protons) indicated the empirical formula $C_9H_{16}O_3$. Infra-red spectroscopy confirmed the presence of a non-conjugated ester group absorbing at 1740 cm^{-1}. The ^{1}H-NMR. spectrum revealed the nature and the relative position of the third oxygen atom with respect to the ester function. The presence of the partial structure $CH_3-\underset{|}{C}H-O-\underset{|}{C}H-CH_2-COOCH_3$ was suggested by signals at δ 1.14 (*d*, $J=6.5$ 3 H, $CH_3-CH-O-$); 3.47 (*m*, 1 H, $CH_3-CH-O-$); 3.69 (*s*, 3 H, $-COOCH_3$); 3.80 (*m*, 1 H, $-O-CH-CH_2COO-$). The methylene protons next to the ester function appeared as the *AB* part of an *ABX* system with $\delta_A=2.40$, $\delta_B=2.58$, $J_{AB}=15$ Hz, $J_{AX}=6$ Hz, $J_{BX}=7$ Hz. Irradiation at the center of this signal resulted in a simplification of the *m* at 3.80, and irradiation at 3.47 changed the *d* at 1.14

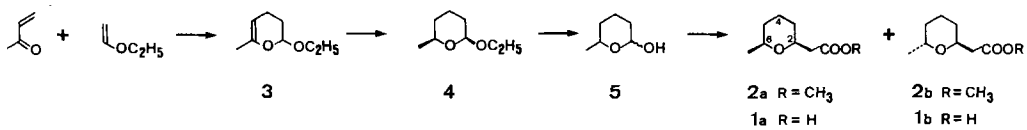
[1]) Civet is the glandular secretion from the civet cat *(Viverra civetta)*. Together with ambergris, castoreum and musk, it is one of the few very expensive animal perfume materials [1].

[2]) **1a** has a very faint sour-fatty odour.

into a *s*. With the partial structure accounting for $C_6H_{10}O_3$ and no further methyl group being present, the remaining C_3H_6 unit must be part of a tetrahydropyran ring, the latter being in good agreement with the mass spectrum of **2a**. Besides the parent ion (*m/e* 172), the base peak appears at *m/e* 116 and an important *α*-cleavage ion at *m/e* 99. Both fragment ions are typical for 2-substituted tetrahydropyrans and have been explained as shown [2].



In order to confirm the structure and to assign the relative configuration of the natural product[3]), the two racemic diastereoisomers, **2a** and **2b**, were synthesized by the following route.



Catalytic reduction of the *Diels-Alder* adduct **3** of methyl vinyl ketone and ethyl vinyl ether using *Raney* nickel and hydrogen at 300 atm proceeded stereoselectively to give a 63% yield of the kinetically controlled *cis* compound **4** [3] [4][4]). This product is the less stable isomer and equilibrates at 20° within a few hours in ethanol containing a trace of hydrochloric acid, furnishing an equilibrium mixture of both anomers (*cis/trans* ratio *ca.* 1:2, in agreement with the reported value of 34.5% *cis* [4]). Hydrolysis of **4** with 0.2 N aqueous HCl gave a 55.7% yield of the anomeric mixture **5** (*cis/trans ca.* 3:2, see exper. part) the separation of which was not attempted. Treatment of **5** with methyl dimethylphosphonoacetate in the presence of sodium methoxide yielded an equilibrium mixture[5]) (86.3%) of the *cis* and the *trans* esters **2a** and **2b** (*ca.* 7:1) which were separated by distillation. The more abundant isomer, **2a** (lower boiling and shorter retention time on a silicone column), proved identical (spectral data and GC.) with the methyl ester of the natural product. Alkaline hydrolysis of **2a** and **2b** led, without noticable epimerization *via β*-elimination, to the free carboxylic acids **1a** and **1b**, respectively.

The configurational assignment of esters **2a** and **2b** is based on the following. (1) An anomeric effect being absent, the more stable isomer **2a** should have both of its substituents equatorial in the more stable chair conformation and thus be *cis*. (2) The less stable *trans* isomer **2b** should exist at room temperature as two rapidly equilibrating chair conformations, the two protons at C(2) and C(6) giving rise to an *ax/eq* time averaged signal in the ^{1}H-NMR. spectrum. Accordingly, the

3) The amount of **2a** was too small for optical rotation to be measured.

4) Other workers [3] obtained a 1:1 mixture of both the *cis* compound **4** and the corresponding *trans* isomer under similar conditions. Their result is probably due to partial acid-catalyzed equilibration during work-up.

5) Equilibration of the pure less stable *trans* ester **2b** under the reaction conditions led to the same mixture (7:1) of **2a** and **2b**.

two axial methine protons of the *cis* ester **2a** resonate at higher field (δ 3.47 and 3.80 ppm) than the corresponding protons of the *trans* isomer **2b** (δ 3.96 and 4.28 ppm). (3) In the ^{13}C-NMR. spectrum of the *trans* acid **1b**, the signal for C(4) is observed at 18.2 ppm as compared to 23.4 ppm for the *cis* acid **1a**. This difference must be due to the γ-effect caused by the axial substituent present in both of the chair conformations of the *trans* acid **1b**.

Experimental Part

General. ^{1}H-NMR. spectra were recorded on a *Bruker* HX 90/15″ instrument (90 MHz) and ^{13}C-NMR. spectra on a *Bruker* WH 360 instrument (90.52 MHz), using $CDCl_3$ as solvent. Chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane as an internal standard; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quartet, *m* = multiplet, br. = broad, *J* = spin-spin coupling constant (Hz), $w_{1/2}$ = half-width (Hz). Mass spectra were recorded on an *Atlas* CH 4 mass spectrometer, using an inlet temperature of *ca.* 150° and electrons of *ca.* 70 eV energy; the intensity of the molecular ion (M^+) and of the eight most intense fragment ions are given in % of the most abundant peak. IR. spectra were recorded on a *Perkin-Elmer* 720 spectrometer; absorption maxima are given in cm^{-1}; abbreviations: *s* = strong, *m* = medium, *w* = weak, sh = shoulder. Gas chromatography (GC.) was carried out on a *Varian Aerograph* series 1800 instrument, using Carbowax 20 M, 5% on Chromosorb W 95, 60–80 mesh (4 mm × 4 m) and silicone GE XE-60, 10% on Chromosorb G (acid washed, DMCS treated), 80–100 mesh (4 mm × 1.5 m). Abbreviations: RT. = room temperature, aq. = aqueous.

Isolation from Civet. Distillation[6]) of commercial crude natural civet in a simple distillation apparatus gave a distillate (10.5%, including the material collected in the cooling trap at *ca.* −180°), b.p. < 110°/0.005 Torr, containing a large amount of water. A tenfold amount of ether was added to the distillate and this was extracted at *ca.* 5° with 4 portions of aq. 10% Na_2CO_3-solution. The alkaline aq. phase was washed with ether, carefully acidified with aq. 30% sulfuric acid, saturated with NaCl, and extracted several times with ether. The extract was washed with brine, dried (Na_2SO_4), and the solvent distilled. The crude volatile acids (0.96%) were esterified with etheral diazomethane and distillation of the methyl esters through a *Fischer* column MS 200 (*ca.* 40 theoretical plates) gave a fraction (0.088%), b.p. 74–78°/10 Torr, containing methyl octanoate and methyl phenylacetate as main components, and methyl nonanoate, methyl decanoate, and methyl (*cis*-6-methyltetrahydropyran-2-yl)-acetate (**2a**) as minor components. Ester **2a** (retention time slightly shorter than methyl decanoate on Carbowax) was isolated by preparative GC. and had the same spectral data and retention time as the synthetic material[3]).

cis-*2-Ethoxy-6-methyltetrahydropyran* (**4**). 2-Ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (58.0 g, 0.408 mol) [5] in 20 ml of ethanol was hydrogenated in the presence of 5 g of *Raney* nickel (*Degussa*, Type B 114) at 60° for 20 h in an autoclave at 300 atm. The catalyst was removed by filtration and the ethanol distilled at atmospheric pressure. Distillation of the residue through a *Vigreux* column gave 37.1 g (63%) of a single product, b.p. 48–50°/10 Torr, shown to be the *cis* isomer by NMR. Surprisingly, only traces if any of the *trans* isomer could be detected by GC. and NMR. (*cf.* [3]). – IR. (neat): 1460*m*, 1445*m*, 1375*s*, 1320*m*, 1210*m*, 1175sh, 1160*s*, 1135*s*, 1090sh, 1075*s*, 1035*s*, 995*s*, 960*m*, 895*m*, 870*m*, 840*m*, 805*w*. – ^{1}H-NMR.: 1.22 (*d*, *J* = 6.5, 3 H, CH_3–C(6)); 1.23 (*t*, *J* = 7, 3 H, OCH_2CH_3); 3.51 (*m*, 2 H, OCH_2CH_3); 3.95 (*d* × *qa*, *J* = 9 and 6.5, 1 H, H–C(6)); 4.40 (*d* × *d*, *J* = 9 and *ca.* 2, 1 H, H–C(2)). – MS.: 144 (M^+, 6), 143 ($M^+ - 1$, 12), 75 (100), 47 (86), 42 (68), 72 (59), 55 (49), 70 (45), 43 (33).

cis *and* trans-*2-Hydroxy-6-methyltetrahydropyran* (**5**). *cis*-2-Ethoxy-6-methyltetrahydropyran (**4**) (33.0 g, 0.229 mol) was boiled for 2 h with aq. 0.2N HCl. The mixture became homogeneous and was neutralized with aq. 1N NaOH (phenolphthalein), saturated with NaCl, and extracted several times with ether. After evaporation of the ether, distillation of the product through a *Vigreux* column gave 14.8 g (55.7%) of hemiacetal **5**, b.p. 69–76°/10 Torr, shown to be a mixture of the *cis* (60%) and the *trans* isomer (40%). This ratio was determined by the integral of the signals for the anomeric protons, the signal for the *cis* compound being a broad doublet at 4.71 ppm (*J* = 9) and for the *trans* isomer a broad singlet at 5.29 ppm ($w_{1/2}$ = *ca.* 5).

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[6]) Treatment of undistilled civet with aq. base resulted in the formation of stable emulsions.

*Methyl (*cis- *and* trans-*6-methyltetrahydropyran-2-yl)acetates* (**2a**) *and* (**2b**). To a mixture of hemiacetal **5** (14.3 g, 0.123 mol; 3:2 mixture of anomers) and methyl dimethylphosphonoacetate (67.3 g, 0.370 mol) was added with stirring at RT. a methanolic solution of sodium methoxide (0.370 mol, prepared by dissolving 8.51 g of sodium in 170 ml of dry methanol). The mixture was stirred overnight under gentle reflux and the main part of the methanol was removed by distillation. The residue was poured into water, acidified with aq. 10% HCl-solution and extracted 3 times with ether. The etheral extract was washed (saturated aq. $NaHCO_3$-solution and brine), dried (Na_2SO_4), concentrated, and distilled through a *Vigreux* column (10 cm) giving 18.3 g (86.3%) of a mixture of the *cis* **2a** and the *trans* ester **2b** (ratio *ca.* 7:1), b.p. 84–88°/10 Torr. Redistillation using a *Fischer* column MS 200 (*ca.* 40 theoretical plates) gave 10.9 g of pure *cis* ester **2a** (bath temperature 92°/10 Torr) and 1.35 g of 95% pure *trans* ester **2b** (bath temperature 100°/10 Torr). The latter was obtained pure by prep. GC. (silicone 150°). The *cis* compound **2a** (with shorter retention time on silicone) exhibited the same spectral and chromatographic data as the methyl ester prepared from the naturally occurring acid **1a**.

Spectral data of cis *ester* **2a**. – IR. (neat): 1740*s*, 1630*w*, 1435*m*, 1370*m*, 1345*m*, 1285*m*, 1250*m*, 1200*s*, 1170*s*, 1085*m*, 1070*s*, 1040*m*, 1000*m*, 960*w*, 910*w*, 870*w*, 845*w*, 795*w*. – ^{1}H-NMR.: 1.14 (*d*, J=6.5, 3 H, H_3C–C(6)); 2.49 (*AB* part of *ABX* system with δ_A=2.40, δ_B=2.58, J_{AB}=15, J_{AX}=6, J_{BX}=7, 2 H, CH_2COO); 3.47 (*m*, 1 H, H–C(6)); 3.69 (*s*, 3 H, OCH_3); 3.80 (*m*, 1 H, partly hidden, H–C(2)). – MS.: 172 (M^+, 6), 116 (100), 43 (90), 99 (87), 41 (71), 129 (67), 55 (67), 42 (66), 74 (62).

Spectral data of trans *ester* **2b**. – IR. (neat): 1735*s*, 1630*w*, 1440*m*, 1380*m*, 1285*s*, 1260*m*, 1210*s*, 1200 sh, 1165*s*, 1135*m*, 1120*m*, 1100*m*, 1085*m*, 1045*s*, 1020*m*, 1010 sh, 945*w*, 900*w*, 850*w*, 840*w*, 775*w*. – ^{1}H-NMR.: 1.19 (*d*, J=6.5, 3 H, H_3C–C(6)); 2.58 (*AB* part of *ABX* system with δ_A=2.46, δ_B=2.70, J_{AB}=15, J_{AX}=6.5, J_{BX}=8, 2 H, CH_2COO); 3.71 (*s*, 3 H, OCH_3); 3.96 (*m*, 1 H, H–C(6)); 4.28 (*m*, 1 H, H–C(2)). – MS.: 172 (M^+, 3), 99 (100), 43 (95), 81 (81), 55 (80), 116 (75), 41 (68), 42 (56), 129 (52).

*(*cis-*6-Methyltetrahydropyran-2-yl)acetic acid* (**1a**). To a solution of the *cis* ester **2a** (2.0 g, 11.36 mmol) in 5 ml of methanol were added 20 ml of aq. 10% NaOH-solution. The mixture was stirred under reflux for 3 h, washed with ether, acidified with aq. 10% HCl-solution, saturated with NaCl, and extracted with ether. Recrystallisation (pentane, 0°) of the residue of the etheral extract gave 1.75 g (95%) of pure *cis* acid **1a**, m.p. 52–53° (not corrected). – IR. ($CHCl_3$): 3700*w* (br.), 3550*m* (br.), 3400–2400*s* (br.), 1750*s*, 1710*s*, 1440*m*, 1410*m*, 1370*m*, 1290*m*, 1190*m*, 1175*m*, 1140*m*, 1085*m*, 1065*s*, 1040*m*, 995*m*, 960*w*, 940*w*, 900*w*, 870*w*, 845*w*. – ^{1}H-NMR.: 1.22 (*d*, J=6.5, 3 H, CH_3); 2.56 (*AB* part of *ABX* system with δ_A=2.53, δ_B=2.58, J_{AB}=15, J_{AX}=5, J_{BX}=8, 2 H, CH_2COO); 3.58 (*m*, 1 H, H–C(6)); 3.80 (*m*, 1 H, H–C(2)); *ca.* 9.9 (br., 1 H, COOH); irradiation at 1.22 ppm simplified the *m* at 3.58 ppm. – ^{13}C-NMR.: 22.0 (*qa*, CH_3); 23.4 (*t*, C(4)); 30.9 (*t*, C(3)); 32.9 (*t*, C(5)); 41.4 (*t*, CH_2COO); 74.1 (*d*, C(2) or C(6)); 74.4 (*d*, C(6) or C(2)); 176.2 (*s*, COO). – MS.: 158 (M^+, 8), 42 (100), 55 (91), 43 (86), 102 (73), 41 (69), 45 (64), 86 (52), 60 (46).

*(*trans-*6-Methyltetrahydropyran-2-yl)acetic acid* (**1b**). Repeating the above-mentioned procedure with the *trans* ester **2b** gave the pure *trans* acid **1b** as a viscous liquid (98% yield) which could not be crystallized. – IR. (neat): 3600–2400*s* (br.), 1735*s*, 1710*s*, 1445*m*, 1410*m*, 1380*m*, 1295*s*, 1265*m*, 1210*s*, 1200 sh, 1175*s*, 1135*m*, 1120*m*, 1085*m*, 1045*s*, 1010*s*, 950*w*, 850*w*, 780*w*. – ^{1}H-NMR.: 1.23 (*d*, J=6.5, 3 H, CH_3); 2.62 (*AB* part of *ABX* system with δ_A=2.51, δ_B=2.73, J_{AB}=15, J_{AX}=5, J_{BX}=8, 2 H, CH_2COO); 4.03 (*m*, 1 H, H–C(6)); 4.26 (*m*, 1 H, H–C(2)); 7.53 (br., 1 H, COOH); upon irradiation at 1.23 ppm the *m* at 4.03 ppm turned into a broad *s*. – ^{13}C-NMR.: 18.2 (*t*, C(4)); 19.4 (*qa*, CH_3); 29.6 (*t*, C(3)); 31.2 (*t*, C(5)); 38.9 (*t*, CH_2–COO); 67.9 (2×*d*, C(2) and C(6)); 176.2 (*s*, COO). – MS.: 158 (M^+, 3), 55 (100), 43 (94), 42 (92), 41 (70), 81 (59), 45 (54), 102 (52), 99 (46).

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