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IMIDAZOLYLCARDENOLIDES

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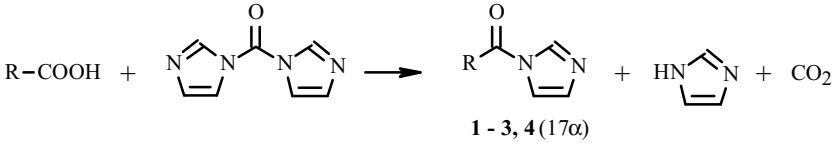
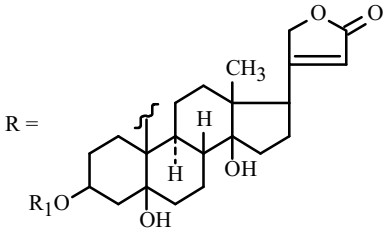
*The new compounds strophanthidin-19-carbonylimidazole (**1**), erysimin-19-carbonylimidazole (**2**), cymarin-19-carbonylimidazole (**3**), and 17α-strophanthidin-19-carbonylimidazole (**4**) were synthesized by reacting cardenolide carboxylic acids and* N,N′*-carbonyldiimidazole. It was shown for the first time that this reaction can be carried out with an angular carboxylic acid. The preparation and previously unknown properties of erysimin-19-carboxylic acid, cymarin-19-carboxylic acid, and 17α-strophanthidin-19-carboxylic acid were also described.*

Key words: cardenolide-19-carboxylic acids, *N*,*N*′-carbonyldiimidazole, CDI, strophanthidin, erysimin, cymarin.

The goal of our work was to prepare new biologically active compounds and to demonstrate in principle the ability of an angular carboxylic acid to react with *N*,*N*′-carbonyldiimidazole (CDI). The results showed that the reaction of carboxylic acids with CDI followed the scheme and was also suitable if cardenolides containing an angular C-19-carboxylic acid were used.



1 - 3, 4 (17α)



1: R_1 = H; **2**: R_1 = β-D-digitoxose; **3**: R_1 = β-D-cymarose;
4: R_1 = H, 17α-strophanthidin-19-carbonylimidazole

We used for the reaction strophanthidin-19-carboxylic acid, 17α-strophanthidin-19-carboxylic acid, erysimin-19-carboxylic acid, and cymarin-19-carboxylic acid that were prepared beforehand by oxidation of the angular aldehyde in the corresponding cardenolides (see Experimental).

The syntheses were carried out in anhydrous organic solvents that were inert to CDI. The reaction temperature was kept below 70°C because the target products were comparatively unstable to heating. The course of reactions was monitored using TLC. The products were purified over columns of silica gel to produce the new compounds **1**-**4**, the structures of which were confirmed by elemental analyses and spectral studies. The IR spectrum of the imidazole moiety had characteristic series of overlapping bands in the range 2872-2997 cm^{-1}. The PMR spectrum of this moiety gave three 1H-singlets at 8.15-8.35 ppm (2′-H), 7.25-7.65 (4′-H), and 7.03-7.10 (5′-H). This agreed with the literature [1].

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EXPERIMENTAL

The course of reactions and the purity of products were monitored using TLC on Sorbfil plates, $CHCl_3$:CH_3OH (9:1) solvent, and Raymond reagent developer (for cardenolides [2]). Elemental analyses were performed in a model 1106 automated C—H—N—S analyzer. All analyses corresponded with those calculated.

PMR spectra in DMSO-d_6 were obtained on a Varian Mercury VX-200 spectrometer (200 MHz) with Me_4Si internal standard; IR spectra in KBr disks, on a Bruker Tensor-27 spectrometer; mass spectra, in a Varian 1200L spectrometer (direct sample introduction into the source, EI, 70 eV).

Erysimin-19-carboxylic Acid. Erysimin (5 g) was dissolved in acetone (100 mL), treated with constant stirring over 8 h with small portions of finely ground potassium permanganate (3.7 g), and left overnight at 2-4°C. The resulting dark-brown precipitate was separated, washed with cold acetone, and dried. Yield 8.5 g. The acetone solution was evaporated in vacuo. The resulting solid was combined with the precipitate. The solid was treated with $CHCl_3$:EtOH (2:1, 100 mL) and H_2SO_4 (10%) until the pH was ~3.0, stirred for 7 min, and filtered. The lower phase was separated. The upper phase was extracted with $CHCl_3$:EtOH (2:1, 2 × 30 mL). The combined $CHCl_3$:EtOH solution was washed with water (3 × 20 mL) and evaporated in vacuo to afford amorphous powder (4.5 g) that was crude erysimin-19-carboxylic acid that was purified by conversion to the ammonium salt as follows. It was dissolved in $CHCl_3$:EtOH (2:1, 150 mL), cooled with ice, treated with cold aqueous ammonia (40 mL, 5%), and stirred for 3 min. The lower organic phase was separated. The upper phase was extracted with $CHCl_3$:EtOH (2:1, 40 mL). The upper phase was neutralized with H_2SO_4 (10%) and then acidified to pH ~3.0. Erysimin-19-carboxylic acid was extracted from the solution by $CHCl_3$:EtOH (2:1, 2 × 150 mL). The $CHCl_3$:EtOH solution was washed with water (4 × 20 mL) and evaporated in vacuo. The solid (4.1 g) was crystallized from CH_3OH:Et_2O to afford pure crystalline erysimin-19-carboxylic acid (3.7 g), $C_{29}H_{42}O_{10}$, mp 155-157/167-172°C; $[\alpha]_D$ +44.8 ± 2°(*c* 1.0, CH_3OH).

Cymarin-19-carboxylic acid was prepared by oxidation of cymarin analogously as described above for oxidation of erysimin, $C_{30}H_{44}O_{10}$, mp 155-157°C, $[\alpha]_D$ +48.3 ± 2° (*c* 1.2, CH_3OH).

The two other acids, strophanthidin-19-carboxylic and 17α-strophanthidin-19-carboxylic, were prepared by the method described above. Their properties are known.

17α-Strophanthidin-19-carboxylic acid was prepared analogously by the oxidation of 17α-strophanthidin, $C_{23}H_{32}O_7$, mp 210-214°C, $[\alpha]_D$ +42.6 ± 2° (*c* 0.8, CH_3OH).

The properties of strophanthidin-19-carboxylic acid prepared by oxidation of strophathidin are known, have been published by us earlier [3], and are in agreement.

Strophanthidin-19-carbonylimidazole (1). Strophanthidin-19-carboxylic acid (1.3 g) and CDI (0.5 g) were dissolved in anhydrous dioxane (5 mL), heated for 2 h at 68-70°C, and evaporated in vacuo. The solid was chromatographed over a column of silica gel (52 g, 0.04-0.06 mm) with elution by $CHCl_3$ and $CHCl_3$:CH_3OH of increasing polarity. Fractions containing pure **1** were combined, evaporated, and crystallized from $CHCl_3$:hexane to afford crystalline **1** (0.4 g), $C_{26}H_{34}N_2O_6$, mp 268-270/275-277°C, $[\alpha]_D$ −33.7 ± 3° (*c* 0.7, $CHCl_3$:CH_3OH).

PMR spectrum (δ, ppm): 0.90 (3H, s, 18-CH_3), 4.95 (2H, t, 21-CH_2), 6.0 (1H, s, 22-H), 7.05 (1H, s, 5′-H), 7.30 (1H, s, 4′-H), 8.15 (1H, s, 2′-H).

Mass spectrum (*m*/*z*, I_{rel}, %): 396 (8) $[M - C_3H_4N_2 + 2H]^+$, 366 (7) $[M - C_3H_4N_2 - CO]$, 340 (15) $[366 - CO + 2H]^+$, 256 (7) $[M - C_3H_4N_2 - CO - 110]$, 231 (100), 215 (16), 208 (56), 203 (10), 197 (19), 195 (21), 190 (34), 185 (24), 160 (47), 146 (36), 133 (28), 131 (47), 111 (30), 107 (20), 105 (50), 91 (67), 83 (21), 82 (22), 79 (37), 67 (23).

IR spectrum (ν, cm^{-1}): 2872-2997 (series of overlapping bands, imidazole), 1610 (C=C), 1729 (butenolide ring C=O).

17α-Strophanthidin-19-carbonylimidazole (4) was synthesized starting with 17α-strophanthidin-19-carboxylic acid and was purified by chromatography over a column as described above for **1**, $C_{26}H_{34}N_2O_6$, mp 220-222°C, $[\alpha]_D$ −5.3 ± 2° (*c* 1.2, CH_3OH).

PMR spectrum (δ, ppm): 0.80 (3H, s, 18-CH_3), 4.90 (2H, t, 21-CH_2), 5.85 (1H, s, 22-H), 7.03 (1H, s, 5′-H), 7.65 (1H, s, 4′-H), 8.35 (1H, s, 2′-H).

Mass spectrum (*m*/*z*, I_{rel}, %): 396 (10) $[M - C_3H_4N_2 + 2H]^+$, 366 (5) $[M - C_3H_4N_2 - CO]$, 340 (28), 231 (58), 215 (15), 211 (11), 203 (8), 197 (17), 190 (20), 187 (49), 161 (42), 160 (96), 145 (40), 131 (54), 105 (68), 91 (100), 79 (52), 67 (22).

Erysimin-19-carbonylimidazole (2) was synthesized from erysimin-19-carboxylic acid and purified analogously as above, $C_{32}H_{44}N_2O_9$, $[\alpha]_D$ + 7.6 ± 2° (*c* 1.8, CH_3OH).

PMR spectrum (δ, ppm): 0.85 (3H, s, 18-CH_3), 4.90 (2H, t, 21-CH_2), 5.95 (1H, s, 22-H), 7.1 (1H, s, 5′-H), 7.25 (1H, s, 4′-H), 8.15 (1H, s, 2′-H).

Mass spectrum (*m*/*z*, I_{rel}, %): 534 (5) [M - $C_3H_4N_2$ + H]$^+$, 506 (7) [M - $C_3H_4N_2$ - CO], 475 (7) [506 - 131 (D-digitoxose)], 366 (6), 340 (18), 197 (19), 187 (25), 179 (17), 160 (68), 145 (32), 131 (43), 119 (36), 111 (29), 105 (57), 95 (36), 91 (100), 81 (31), 79 (53), 77 (36), 67 (36).

Cymarin-19-carbonylimidazole (3) was synthesized analogously to **1**, $C_{33}H_{46}N_2O_9$, $[\alpha]_D$ + 12.7 ± 3° (*c* 0.7, $CHCl_3$:CH_3OH).

PMR spectrum (δ, ppm): 0.83 (3H, s, 18-CH_3), 3.2 (3H, s, OCH_3), 4.95 (2H, t, 21-CH_2), 6.0 (1H, s, 22-H), 7.05 (1H, s, 5′-H), 7.30 (1H, s, 4′-H), 8.15 (1H, s, 2′-H).

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