SYNTHESIS AND CHIROPTICAL PROPERTIES OF 5α-CHOLEST-2-ENO[2,3-b]PYRAZINE DERIVATIVES

Gyorgy Hajős[+] and Günther Snatzke*

Ruhr-Universität Bochum, Lehrstuhl für Strukturchemie,
Postfach 10 21 48, D-4630 Bochum 1 (F.R. Germany)

Dedicated to Prof. Sir Derek Barton
on the Occasion of His Seventieth Birthday

Abstract - The steroidal pyrazine **5** has been synthesized from 5α-cholestane-2,3-dione, and its cd has been compared with that of octahydronaphtopyrazine **7** with C_2-symmetry. The n→π* - Cotton effects of the parent compound have the same signs and magnitudes as for the homochirally analogous steroid, whereas the π→π* - Cotton effects differ. On the other hand, pyrazines containing substituents nonsymmetrically attached to the chromophore show very similar Cotton effects. Assignment of transitions for the 2,3-dihydropyrazine chromophore could be made by comparison of the cd and uv spectra.

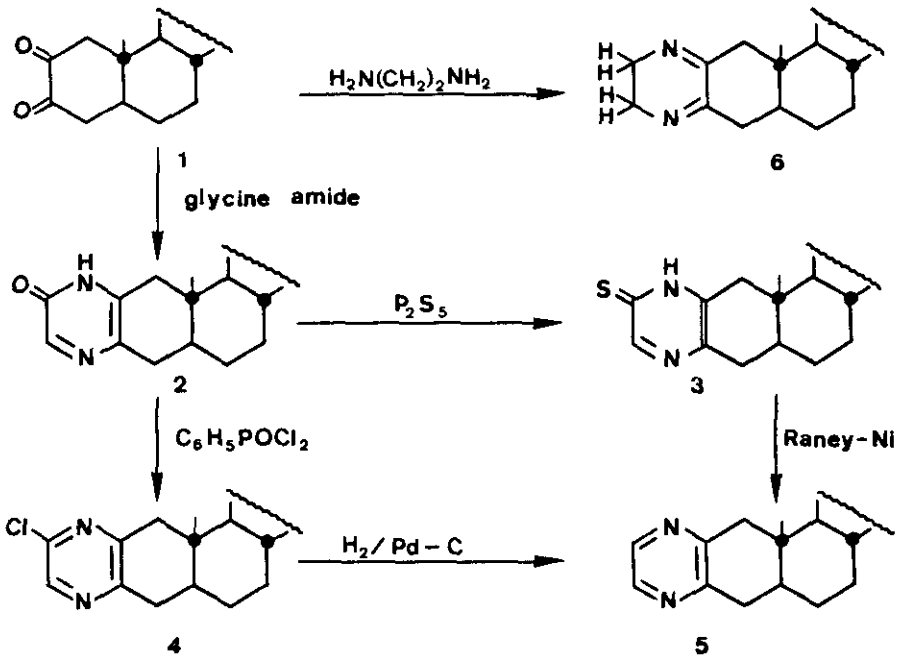
Previously we published[1,2] on the synthesis and chiroptical properties of octahydronaphtho-[2,3-b]pyrazine and some of its derivatives. This molecule has C_2-symmetry and it was thus interesting to investigate whether the lowering of symmetry and especially the presence of an axial methyl group at the angular position will change the magnitudes and/or signs of the Cotton effects, as it had been observed for analogous steroidal furanes and thiophenes.[3,4] To this end we synthesized the title compound and measured its cd and that of some derivatives.

The synthesis of the title compound was accomplished in a similar manner to that used for the related tricyclic system.[1] Thus, 5α-cholestane-2,3-dione (**1**) was first reacted with glycine amide to yield the pyrazinone **2**. Since a routine conversion of this compound to a chloro derivative by phosphorus pentachloride failed we elaborated two other routes for preparation of the desired unsubstituted compound.

[+] A.v.Humboldt-fellow during 1985/86. Permanent address: Central Research Institute for Chemistry, Pusztaszeri Út 59-67, H-1025 Budapest, Hungary.

Compound 2 could be transformed to the thione analogue by using phosphorus pentasulfide, and the rather unstable yellow thio compound **3** was then reduced by Raney nickel[5] in dioxane in poor yield to **5**. Phenylphosphonic acid dichloride also reacted with pyrazinone 2, and the 6'-chloro compound **4** could be isolated in moderate yield; it gave rise to the same product **5** as obtained by the above mentioned reduction, with Pd-C as catalyst for hydrogenation.

Compounds 2 and 3 were not purified by chromatography because of their poor solubilities and instabilities, and were used for further reactions as crude products. The chloro compound **4**, however, proved to be stable enough even for column chromatography, which detected the presence of an additional minor product, too; this could easily be removed by proper crystallization techniques. Because of the asymmetrical steroid skeleton, formation of two isomeric ring-closed products, i.e. the 5'-chloro and 6'-chloro compounds can be envisaged, but only one was formed predominantly. Because of our main interest in the final product **5**, which could be formed by treatment of both possible isomers (either via **3** or **4**), no attempts were made to elucidate the accurate structure of the main product of the ring closure. Mechanistic considerations suggest,however, formation of 2 rather than of the other possible isomer.[6]

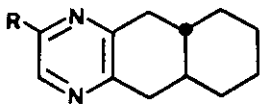


An approach to obtain **5** by a condensation reaction of 5α-cholestane-2,3-dione (**1**) and 1,2-diaminoethane followed by oxidation proved to be unsuccessful. Although this reaction provided 5',6'-dihydro-5α-cholest-2-eno[2,3-b]pyrazine (**6**) as brilliant crystals in good yield, this latter product[7] was found to be unreactive against different oxidizing agents.[8] This interesting stability of some dihydropyrazines is well known from literature.[9]

Pyrazines (e.g. 7) show four Cotton effects between 350 and 200 nm as depicted in Fig. 1.[2] The first and third correspond to the $n^+ \rightarrow \pi_4^*$ - and $n^- \rightarrow \pi_4^*$ - transition, resp., the second and fourth had been assigned to the $\pi_3 \rightarrow \pi_4^*$ - and the $\pi_2 \rightarrow \pi_4^*$ - transitions. For **5** we also found four Cotton effects, whose positions are similar to those of **7**, but only the signs and magnitudes of those two cd - bands which correspond to the $n \rightarrow \pi^*$ - transitions remain unchanged, whereas the other two inverted their signs. Similarly to the much better investigated ketones we observe thus also here that the $n \rightarrow \pi^*$ - transitions can much safer be correlated with the absolute configuration of the molecules than the $\pi \rightarrow \pi^*$ - transitions. As in the case of the mentioned furans and thiophenes the signs and magnitudes of the $\pi \rightarrow \pi^*$ - Cotton effects are strongly influenced by the presence of the angular methyl in axial conformation in ß-position to the chromophore.

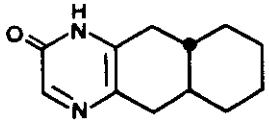
In contrast to the case of the pair **5/7**, the cd spectra of the homochiral analogues **4** and **8** (see Table I) are very similar to each other in shape and in magnitude. This indicates that with a strong perturber like the Cl-atom, which is furthermore not situated on a symmetry axis, the influence of the aforementioned methyl C-19 can be neglected.

Similar results were obtained for the analogues **2** and **9** (Table I), although different solvents had to be used because these amides are sparingly soluble. Nevertheless, the cd spectra are very similar to each other. Positive Cotton effects appear around 340/350 nm and 300/293 nm, and a third, also positive Cotton effect is detectable at still shorter wavelengths (Table I). The same argumentation as above applies: with a less symmetric chromophore the influence of the angular methyl C-19 is not significant.



7 R = H

8 R = Cl



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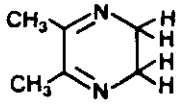

10

Compound **6** contains the dihydropyrazine chromophore. Literature data[10] concerning study on the related parent compound **10** reported two uv absorptions at 337 nm (ε = 200) and 230 nm (ε = 1740), respectively. Calculations suggested that the first corresponds to the $n^+ \rightarrow \pi_3^*$ -, the second to the $n^- \rightarrow \pi_3^*$ - transition,[11] but some doubts arose, since the second band is more intense than the first one, it should, however, correspond to a forbidden transition of A_2-symmetry. In the cd spectrum of **6** we observed at least four Cotton effects above 200 nm; the first one at 380 nm can without doubt be associated with the $n^+ \rightarrow \pi_3^*$ - transition. The second cd - band at 338 nm does also not co-

incide with a band in the absorption spectrum of **6** and we assign it, therefore, to the $n^{+} \rightarrow \pi^{*}_{4}$ - or the $n^{-} \rightarrow \pi^{*}_{3}$ - transition, or rather to a mixture of both. *The third cd - band is observed at 295 nm* (appearing in the uv spectrum only as a shoulder), and thus is close to the first uv absorption band at 307 nm, so it might be associated with the $\pi_{2} \rightarrow \pi^{*}_{3}$ - transition. The fourth Cotton effect, again positive, *is more than 50 times larger than the third one and is just in between two uv maxima*, thus it could correspond to the second combination of the $n^{+} \rightarrow \pi^{*}_{4}$ - and $n^{-} \rightarrow \pi^{*}_{3}$ - transitions. The shoulder in the uv spectrum around 223 nm does again not coincide with the next Cotton effect *at 211 nm. With such a great difference in magnitude* of the 3. and 4. Cotton effects of opposite signs, the smaller one must be apparently shifted bathochromically as is observed, thus both the cd and the uv spectrum can satisfactorily be explained by these assignments.

Table I

Comparison of Cotton effects of **4** and **8**, and **2** and **9**, resp.

Compound	Solvent	λ_{max} ($\Delta\varepsilon$)		
4	CH_3CN	314 (-0.27)	279 (+1.22)	229 (+3.97)
8	CH_3CN	317 (-0.07)	281 (+1.48)	221 (+4.00)
2	CF_3CH_2OH	348 (+0.36)	294 (+0.54)	
9	CH_3CH_2OH	341 (+0.58)	309 (+0.78)	237 (+1.51)

EXPERIMENTAL PART

Melting points were determined on a Kofler block and are not corrected. Mass spectra were determined by a Varian CH-5 instrument. The ^{1}H- and ^{13}C - nmr spectra were recorded by Bruker WP 80 and Bruker AM 400 spectrometers; ir spectra were measured on a Perkin Elmer 1310, and uv spectra on a Varian Cary 17 spectrometer; cd spectra were recorded with an ISA - Dichrograph Mark III with an attached PDP-8/e computer.

5α-Cholest-2-eno[2,3-b]pyrazin-6'(1'H)-one (2)

To a solution of 5α-cholestane-2,3-dione (**1**, 6.0 g, 15 mmoles) in ethanol (300 ml), a solution of glycine amide hydrochloride (2.4 g, 21.8 mmoles) in 0.4 N methanolic sodium hydroxide (55 ml) was added at room temperature and the mixture was stirred for 12 h. Hydrochloric acid was then added until pH 4 was reached, the mixture was then concentrated to a third of its volume by evaporation in vacuo. The formed cream-coloured precipitate was filtered off and the crude product was washed thoroughly with water and twice with ethanol to yield 5.15 g (78%) of **2**.

For spectroscopic investigations a sample of the crude product was recrystallized from acetic acid to give colourless prisms, mp 318 - 320°C, $[\alpha]_D^{25}$ = + 125 (c = 1.0 g/100 cm^3, $CHCl_3$).

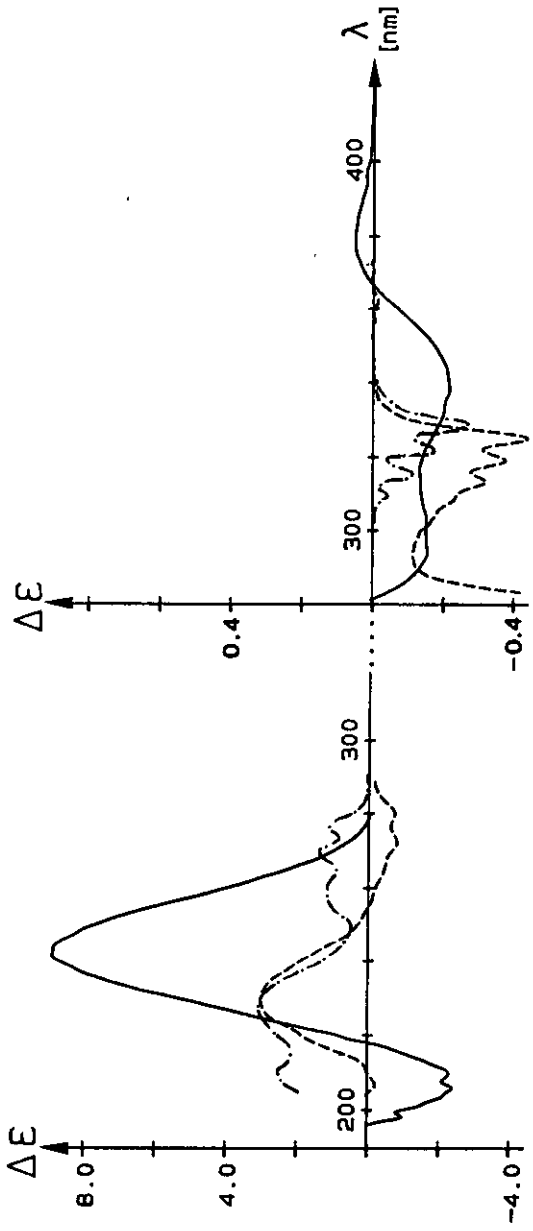

Fig. 1

CD spectra of derivatives with heteroaromatic pyrazine (5 -------, and 7 -.-.-.-.-) and dihydropyrazine (6 ———) chromophore (CH_3CN).

Calcd for $C_{29}H_{46}N_2O$ (438.70): C, 79.40; H, 10.57. Found: C, 79.16; H, 10.28. Ms: 438 ($M^{+\cdot}$), 423, 298, 283 m/z. ^{1}H Nmr (100 MHz, $CDCl_3$, δ[ppm]): 8.05 (s, 1H, H-5), 5.5 (broad s, 1H, NH). Ir (KBr, cm^{-1}): *3000-2800 (CH_n), 1650, 1610, 1510 (C=N, C=C). Uv ($CHCl_3$, λ[nm] (ε)): 333 (2270).*

5α-Cholest-2-eno[2,3-b]pyrazin-6'(1'H)-thione (3)

A mixture of 2 (0.9 g, 2.0 mmoles), phosphorus pentasulfide (1.5 g, 6.8 mmoles), and pyridine (50 ml) was refluxed for one hour. The mixture was poured then onto ice and extracted with dichloromethane. Evaporation of the organic solvent and treatment of the semi-solide residue with methanol resulted in precipitation of deeply yellow crystals, 0.7 g (75%). This product was used as such in crude form for further reactions. Ms: 454 ($M^{+\cdot}$), 439, 314, 299. Relative molar mass calcd for $C_{29}H_{46}N_2S$: 454.77.

6'-Chloro-5α-cholest-2-eno[2,3-b]pyrazine (4)

A mixture of compound 2 (5.3 g, 12.1 mmoles) and phenylphosphonic acid dichloride (50 ml) was stirred at 160°C for one hour. The resulting solution was cooled and added to 200 g of crushed ice. The mixture was occasionally shaken during a period of 30 min and was then extracted with dichloromethane. The residue obtained from the organic phase was eluted with dichloromethane from silica gel. The main product was found in fractions shortly following the impurities running with the front. Recrystallization from ethyl acetate gave colourless needles; 2.8 g (51%), mp 125 - 126°C, $[\alpha]_D^{25}$ = + 89.1 (c=2.0, $CHCl_3$). Calcd for $C_{29}H_{45}N_2Cl$ (457.15): C, 76.19; H, 9.92. Found: C, 76.41; H, 9.96. Ms: 458/456 (3:1, $M^{+\cdot}$), 442, 317, 302. Ir (KBr, cm^{-1}): 3050-2900 (CH_n), 1620, 1510 (C=C,C=N). Uv (CH_3CN, λ[nm] (ε)): *300 (sh, 5500), 295 (sh, 6060), 282 (10800), 212 (9140).*

5α-Cholest-2-eno[2,3-b]pyrazine (5)

Method A:

A mixture of thio compound 3 (0.30 g, 0.66 mmoles), dioxane (10 ml), and freshly prepared Raney nickel (2.0 g) was refluxed for 30 min. During this period the initial yellow colour disappeared. The mixture was then filtered, the evaporation of the filtrate gave pyrazine compound 5, which was recrystallized from acetone: 0.10 g (36%), mp 128 - 130°C.

Method B:

To a solution of 6'-chloro-5α-cholest-2-eno[2,3-b]pyrazine (4, 2.0 g, 4.4 mmoles) in tetrahydrofuran (60 ml), triethylamine (2 ml) and palladium catalyst (110 mg, 10% on charcoal) were added, and the mixture was hydrogenated at atmospheric pressure. Filtration and evaporation of the reaction mixture gave 1.5 g (81%) of crude 5 which was recrystallized from acetone to give colourless crystals, 1.15 g (62%), mp 128 - 130°C, $[\alpha]_D^{25}$ = + 86.3 (c=1.1, $CHCl_3$).

Calcd for $C_{29}H_{46}N_2$ (422.70): C, 82.40; H, 10.97. Found: C, 81.98; H, 10.84. Ms: 422 ($M^{+\cdot}$), 407, 267. ^{1}H Nmr (400 MHz, $CDCl_3$, δ [ppm]): 8.39 (s, 2H, H-2',3'); 2.96 (d, J=17.0 Hz, 1H, H-1ß); 2.83 (dd, J=18.2, 5.3 Hz, 1H, H-4α); 2.62 (dd, J= 18.2, 12.9 Hz, 1H, H-4ß); 2.55 (d, J=17.0 Hz, 1H,

H-1α); 2.1-0.6 (m, 40H). ^{13}C Nmr ($CDCl_3$, δ[ppm]): 152.83 and 152.27 (C-2 and C-3), 141.87 and 141.70 (C-2' and C-3'), 46.23 (C-1). Ir (KBr, cm^{-1}): 3050-2800 (CH_n), 1620, 1450 (C=N, C=C). Uv (i-octane, λ[nm] (ε)): 324 (900), 312 (1200), 277 (9560), 270 (10080), 203 (7150).

5',6'-Dihydro-5α-cholest-2-eno[2,3-b]pyrazine (6)

A mixture of 5α-cholestan-2,3-dione (1, 0.5 g, 1.25 mmoles), ethanol (3 ml), and 1,2-diaminoethane (0.4 ml) was stirred at 60°C for 5 min. From the cooled reaction mixture crystals separated rapidly, which were filtered off and recrystallized from ethyl acetate, affording thus 0.3 g (60%) of 6, mp 158 - 159°C (lit.[6] mp: 160 - 161°C). Ms: 424 ($M^{+\cdot}$), 409, 269. Relative molar mass calcd for $C_{29}H_{48}N_2$: 424.72. Uv (CH_3CN, λ[nm] (ε)): 307 (950), 277 (1400), 215 (4600).

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