Arch. Pharm. (Weinheim) *312*, 192–198 (1979)

Synthesis of some 2′-(3-Oxopregn-4-en-20-yl)oxazolidines and -thiazolidines

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Eingegangen am 23. März 1978

3-Oxopregn-4-ene-20β-carboxaldehyde (**1**) was condensed with several β-aminoalcohols and β-aminothiols to form oxazolidine and thiazolidine derivatives. Condensation of **1** with *o*-aminothiophenol gave the corresponding benzothiazoline **16**, while condensation of **1** with *o*-aminophenol gave the open-chain *o*-hydroxyaldimine **18**.

Synthese einiger 2′-(3-Oxo-pregn-4-en-20-yl)-oxazolidine und -thiazolidine

3-Oxo-pregn-4-en-20β-aldehyd (**1**) wurde mit einer Reihe von β-Aminoalkoholen und -thiolen kondensiert um Oxazolidin- und Thiazolidin-Derivate zu erhalten. Kondensation von **1** mit o-Aminothiophenol ergab das entsprechende Benzothiazolin **16**, während die Kondensation von **1** mit o-Aminophenol das offenkettige o-Hydroxyaldimin **18** ergab.

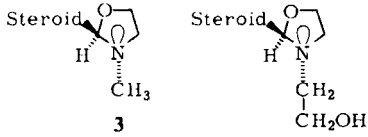
Previous efforts to construct oxazolidine[1–4] or thiazolidine[5–8] rings on steroid skeleton led to pharmacologically active compounds. With one exception,[4] all these examples involved a ring keto group, giving rise therefore to spiranic structures.

To extend existing knowledge in this area, we deemed it of interest to prepare new oxazolidines and thiazolidines attached to the steroidal side chain by bringing 3-oxopregn-4-ene-20β-carboxaldehyde (**1**) to react with various aminoalcohols and aminothiols.

The condensations of **1** with the amino alcohols were effected by azeotropic removal of the water liberated under conditions indicated in Table 1.[9] Free forms of **2** and **8** were found to be unstable, but could be isolated and characterized in their corresponding N-acetyl derivatives **7** and **9**. In the nmr spectrum **2** exhibited a doublet at δ 7.39 ppm (J = 7 Hz 1/2 H) attributable to the aldiminic proton and a broad signal at δ 4.25 ppm (1/2 H) assigned to H 2′ of the oxazolidine ring. From these, and from the presence of two resonances attributable to C-18 methyl group protons in the nmr spectrum of **2** it was inferred that the product from 2-aminoethanol is a mixture of ring-chain tautomers in a ratio of approximately 1 : 1. The spectra of oxazolidines, containing tertiary nitrogen atoms do not show signals around 4.2 ppm. In analogy to

0365-6233/79/0303–0192 $ 02.50/0

1,2-disubstituted pyrrolidines[10–12], it is reasonable to assume that the N-alkyl oxazolidines **3** and **4** should exist as the invertomers delineated below.



3 **4**

The 2′ hydrogens in these structures are situated *trans* to the nitrogen lone pair and *cis* relative to the N-alkyl group. Both relationships are associated with a shielding effect upon H 2′, which may amount to as much as 0.9 ppm[13]. Consequently, it is reasonable to expect that the signal belonging to H-2′ will appear at a higher field, most likely close to the other ring protons.

By contrast, the presence of phenyl and acetyl groups on the nitrogen causes the opposite effect and the signals of H-2′ in **5**, **7** and **9** indeed show up in the range of δ 5.0–5.2 ppm.

Condensation of **1** in aqueous-ethanol with cysteamine and cysteine gave the corresponding thiazolidines **11** and **12**. **11** was converted to the N-acetyl derivative **13**, whereas **12** was esterified to **14** by diazomethane.

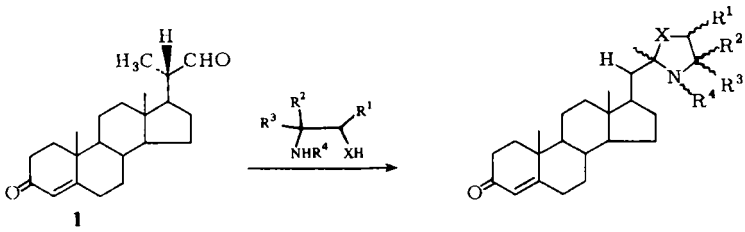
It is worthy of note that the construction of a heterocyclic ring from condensation of the aldehyde group in **1** with an aminoalcohol or aminothiol gives rise to a new chiral center and as a consequence, possibly to pairs of epimeric products. The nmr spectra of some of the products clearly indicate the presence of two epimers, in the other cases the data do not allow to reach definite conclusion concerning the optical purity of the products.

Exception to this are presumably oxazolidines **10** and **15** from the reaction of **1** with ephedrine which is expected to lead to a single product in which the steroid is *trans* related to the methyl and the phenyl groups. The condensation of ephedrine with aromatic aldehydes is known to occur in a stereospecific fashion giving rise to a single stereoisomer the configuration of which was determined by chemical and crystallographic studies[14].

Reaction of o-aminothiophenol with **1** gave the expected benzothiazoline **16**. In contrast the reaction of **1** with o-aminophenol gave mainly progesterone **17**[15]. When this reaction is carried out with the exclusion of air, the corresponding aldimine **18** is formed, as evidenced from its nmr and ir spectral properties.

Pharmacology

Oxazolidines **6** and **7**, as representatives of this series, and thiazolidines **11–13** and **16** were subjected for general pharmacological screening to determine possible central nervous system, cardiovascular, antiarthritic, immunologic, anti-infective and chemo-



1

2 X = O, $R^1 = R^2 = R^3 = R^4 = H$

3 X = O, $R^1 = R^2 = R^3 = H$, $R^4 = CH_2CH_2OH$

4 X = O, $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$

5 X = O, $R^1 = R^2 = R^3 = H$, $R^4 = C_6H_5$

6 X = O, $R^1 = R^2 = H$, $R^2 = R^3 = CH_3$

7 X = O, $R^1 = R^2 = R^3 = H$, $R^4 = COCH_3$

8 X = O, $R^1 = R^2 = R^4 = H$, $R^3 = C_2H_5$

9 X = O, $R^1 = R^2 = H$, $R^3 = C_2H_5$, $R^4 = COCH_3$

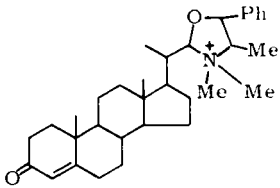
10 X = O, $R^1 = C_6H_5$, $R^2 = H$, $R^3 = R^4 = CH_3$

11 X = S, $R^1 = R^2 = R^3 = R^4 = H$

12 X = S, $R^1 = R^3 = R^4 = H$, $R^2 = CO_2H$

13 X = S, $R^1 = R^2 = R^3 = H$, $R^4 = COCH_3$

14 X = S, $R^1 = R^3 = R^4 = H$, $R^2 = CO_2CH_3$



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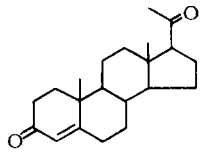
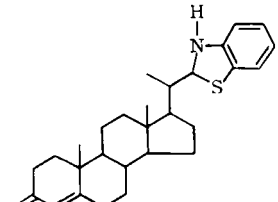
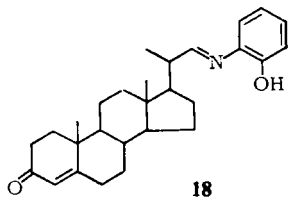


17



16



18

therapy activities. Thiazolidine **12** was found to possess c-AMP phosphodiesterase inhibitory properties in a minimum inhibitory concentration of 50 mg/ml when tested in vitro by a maximal dose of 100 mg/ml.

The other compounds exhibited no meaningful activity.

One of the authors (Y.G.) gratefully acknowledges a generous grant by The National Council for Research and Development of Israel during the early stages of this work.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Jeol C-60-H High Resolution NMR spectrometer (TMS), in $CDCl_3$ unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer Model 237 Grating Infrared Spectrophotometer. UV spectra were measured on a Unicam Ultraviolet Spectrophotometer Model Sp. 800A. $[\alpha]_D$ were measured on a Perkin-Elmer 141 Polarimeter using solutions c = 1,0.

Preparation of Oxazolidines (general procedure)

A solution of **1** and the appropriate aminoalcohol in molar ratios between 1 : 1 and 1 : 2 respectively, was refluxed in benzene, while water was removed (Dean-Stark), under conditions detailed in Table 1. Disappearance of the carbonyl absorption at 1720 cm^{-1}, indicated the completion of the reaction. The benzene and excess of aminoalcohol were evaporated and most of the dry residues were crystallized from solvents cited in Table 2.

Acetylation of Oxazolidines 2 and 8: The formation of Acetooxazolidines 7 and 9.

Crude oxazolidine **2** or **8** was dissolved in acetic anhydride (approcimately 3 ml/mmol starting material). A catalytic amount of pyridine or p-toluenesulfonic acid was added, and the reaction mixture was left overnight at room temp. Completion of the reaction was determined by TLC (silica gel). The reaction mixture was evaporated under reduced pressure and traces of acetic anhydride and acetic acid were evaccuated by successive additions of methanol followed by evaporations. Crude product **7** or **9** was crystallized (Table 2).

General spectroscopic data of the steroidal oxazolidines.

The ranges for the steroidal various methyl hydrogen signals are as follows: δ (ppm) = 0.70–0.74 for 18-CH_3s', 1.17–1.19 for 19-CH_3s' and 0.82–0.98 (J = 6 Hz) for 21-CH_3s'. All products except **15**, showed a molecular ion peak in mass spectra. The existence of the 3-keto-Δ^4 chromophore in steroidal ring A, was proved by the chemical shift of 19-CH_3, the 1660–1670 cm^{-1} and 1600–1610 cm^{-1} bands, in the ir and the λ_{max} at 247 nm ($CHCl_3$) in UV spectra.

20-(1', 3'-thiazolidine-2'-yl)-pregn-4-ene-3-one (**11**)

(I) 3.0 g (9.1 mmol) of **1** were dissolved with heating in 150 ml EtOH. (II) 2.40 g (31.2 mmol) of cysteamine were dissolved in 120 ml of 50 % aqueous ethanol. Solutions I and II were mixed together and the mixture cooled overnight: 1.4 g product, m.p. 202–203 °C. Crystallization of the concentrated filtrate yielded additional 1.3 g product, m.p. 200–202 °C. Total yield was 2.7 g (77 %) $[\alpha]_D$ = +105° ($CHCl_3$). EIMS: m/e 387 (M^+), 124 (base peak); NMR δ (ppm) = 0.73 (s 3H, 18-CH_3), 0.97 [d(J = 6 Hz), 3H, 21-CH_3], 1.16 (s, 3H, 19-CH_3), 2.57–3.10 (m 4H), 3.47 (m 1H), 4.40–4.70 (m 1H), 5.62 (s, 1H, H-4). IR (KBr) 3300, 1655, 1605 cm^{-1}. UV ($CHCl_3$) λ_{max} = 247 nm (ϵ = 6100).

Table 1: *Reaction conditions and yields of steroidal oxazolidines formation*

Oxazolidine	Molar ratio aminoethanol: steroid 1	Solvent	Reaction time (hr)	Yield %
2	1	benzene	2	70
3	2	benzene	18	–
4	1.3	benzene	2	80
5	1.5	xylene	21.5	65
6	1.3	benzene	5	90
8	1.2	benzene	24	90
10	2	benzene	20	60

Table 2: *Physical properties of steroidal oxazolidines*

Compd.	M.P. °C	Solvent of recrystallization	$[\alpha]_D$ (solvent)	Formula	Analysis Calcd. C	H	N	Found C	H	N
3	156–158	EtOH	+81° ($CHCl_3$)	$C_{26}H_{41}NO_3$	75.2	9.88	3.4	75.1	10.11	3.5
4	145–157	benzene-hexane	+72° ($CHCl_3$)	$C_{25}H_{39}NO_2$	77.9	10.13	3.6	77.6	10.28	3.9
5	210–213	EtOH	+87° ($CHCl_3$)	$C_{30}H_{41}NO_2$	80.5	9.17	3.1	80.6	9.44	3.5
6	130–135	hexane	+78° ($CHCl_3$)	$C_{26}H_{41}NO_2$	78.2	10.28	3.5	78.0	10.20	3.5
7	217	MeOH	+85° (EtOH)	$C_{26}H_{39}NO_3$	75.5	9.44	3.4	75.1	9.38	3.6
9	258–263	MeOH	+83° (EtOH)	$C_{28}H_{43}NO_3$	76.2	9.75	3.2	75.9	9.86	3.2

20-(3'-Aceto-1', 3'-thiazolidine-2'-yl)-pregn-4-ene-3-one (13)

0.60 g (1.55 mmol) **1** were dispersed in approximately 10 ml dry pyridine. 1 ml of acetic anhydride was added to the resulting suspension, causing clarification. The reaction mixture was left overnight at room temp., water and ether were added and the product extracted into the organic layer. The ehter combined extracts were washed with additional amounts of water, dried and evaporated under reduced pressure. Crystallization from methanol gave white crystals of **13**, m.p. 212–225 °C. Crystallization of the evaporated filtrate afforded almost pure crystals, m.p. 208–215°. Yield 92 % $[\alpha]_D$ = +134° ($CHCl_3$). EIMS: m/e 429 (M^+), 386 (M-CH_3CO), 130 (base peak). NMR δ (ppm) = 0.74 + 0.76 (s 3H, 18-CH_3's), 0.88 [d (J = 7 Hz), 3H, 21-CH_3], 1.18 (s, 3H, 19-CH_3), 2.13 (s, 3H, CH_3CO-), 5.14 + 5.47 [b + d (J = 3.5 Hz), 1H, – SCH-N-]. IR (KBr) 1670, 1650, 1605, 1235. UV ($CHCl_3$) λ_{max} = 247 nm (ε 16850).

20-(4'-Carboxy-1', 3'-thiazolidine-2'-yl)-pregn-4-ene-3-one **12**

(I) 1.0 g (3mmol) **1** was dissolved by heating in 50 ml of absol. ethanol and cooled to room temp. (II) 0.42 g (3.3 mmol) L-cystein-HCl (anhydrous), and 0.25 g KOAc were dissolved in 10 ml of 50 % aqueous ethanol. (II) was added to (I), and an immediate amorphus white precipitate appeared. The mixture was filtered and the filtrate evaporated to half vol. The resulting vol. of the reaction mixture was cooled overnight and a crystalline yellowish precipitate appeared. After drying, the crystals of **12** melted at 163 °C with decomposition.

Methylation of **12**: 0.18 g (0.42 mmol) **12** (160–163 °C) were dissolved with heating in 50 ml ethanol. After cooling to room temp., excess of diazomethane in ether was added, and the mixture left overnight. Solvents and excess of diazomethane were removed, the residue crystallized from ethanol to give white needles of **14**, m.p. 183–184 °C (yield 50 %). $[\alpha]_D$ = +34° ($CHCl_3$). EIMS: m/e 445 (M^+), 411 (M-CO_2), 146 (base peak). NMR δ (ppm) = 0.73 (s 3H, 18-CH_3), 1.04 [d (J = 6 Hz), 3H, 21-CH_3], 1.17 (s 3H, 19-CH_3). IR: (KBr) 1735 (CH_3OCO-), 1660, 1605 cm^{-1}. UV ($CHCl_3$) λ_{max} = 246 nm (ε = 16300).

20-[N,N-Dimethyl-4'-methyl-5'-phenyl-1', 3'-oxazolidine-2'-ylium)-pregn-4-ene-3-one-iodide (**15**)

0.33 g (1 mmol) **1** and 0.3 g (2 mmol) (–)-ephedrine were dissolved in 30 ml benzene and refluxed overnight while water was removed (Dean-Stark). The benzene and excess of ephedrine were evaporated under reduced pressure.

The crude product **10** was dissolved in 0.4 ml EtOH and a large excess of CH_3I was added. The mixture was stirred and refluxed overnight, resulting in the formation of a white precipitate. After cooling and addition of ether an additional amount of precipitate was obtained. The solvent was removed by decantation, and the precipitate washed with some additional quantities of ether. Trituration of the precipitate with acetone afforded white crystals m.p. 205–210°. Recrystallization from acetone-methanol gave **15**, m.p. 210 °C in 55 % yield. $[\alpha]_D^{25°}$ = +42° ($CHCl_3$). EIMS: m/e 476–477 [M-CH_3 + 1], 326, 313. NMR: ($CDCl_3$) δ (ppm) = 1.21 (s 3H, 19-CH_3), 3.52 (s 3H, CH_3), 3.71 (s 3H, CH_3), 4.88 (bs 1H), 5.99 [b d (J – 6 Hz), 1H], 5.72 (b 1H), 7.27 (m 5H, Arom.). IR (KBr) 1675 (ν C=O), 1655, 1605, 925, 860, 795, 745, 715 cm^{-1}. UV ($CHCl_3$) λ_{max} = 247 nm (ε 23200).

20-(1', 3'-Benzothiazoline-2'-yl)-pregn-4-ene-3-one (**16**)

(I) – 0.5 g (1.5 mmol) **1** were dissolved by heating in 25 ml ethanol. (II) – 0.5 g (4 mmol) o-aminothiophenol were dissolved in 10 ml ethanol. Solution (I) was added to solution (II), and after addition of water until turbidity appeared, the resulting mixture was cooled overnight. The resulting precipitate was washed with hot methanol. The yellowish crystals **16** were dried, m.p. 188–190 °C (yield 57 %). The filtrate contained additional quantity of **16**. $[\alpha]_D$ = +139.5° ($CHCl_3$). EIMS: m/e 433 [M-2], 163 (base peak), 136. NMR δ (ppm) = 0.74 (s 3H, 18-CH_3), 1.10 [d (J = 6 HZ), 3H, 21-CH_3], 1.18 (s 3H, 19-CH_3), 5.55 (b s 1H, -S-CH-N-), 6.35–7.10 (m 4H, Arom.). IR: (KBr) 3350, 1665, 1610, 158, 740 cm^{-1}. UV ($CHCl_3$) λ_{max} = 246 (ε = 20770), 316 nm (ε = 3900).

Reactions between **1** *and o-aminophenol*

a) 1.0 g (3 mmol) **1** and 0.327 g (3 mmol) of o-aminophenol in 50 ml $CHCl_3$ were refluxed for 2 hrs, and water was removed azeotropically during the reaction. The $CHCl_3$ was evaporated, and the crude product separated on aluminium oxide preparative TLC plates ($CHCl_3$:CCl_4 1:1). The main product was crystallized from CH_3OH to afford crystals, m.p. 125° identified as progesterone (**17**). EIMS: m/e 314 (M^+), 299 [M-CH_3], 229 (base peak). NMR: ($CDCl_3$) δ (ppm) = 0.67 (s 3H, 18-CH_3), 1,21 (s 3H, 19-CH_3), 2.15 (s 3H, 21-CH_3), 5.82 (s 1H, H-4). IR: (neat) 1700 (ν C=O), 1670 (ν C=O), 1610 (C=C). b) A solution of 1.0 g (3mmol) **1** and 0.4 g (3.7 mmol) o-aminophenol in 50 ml $CHCl_3$ was refluxed for 1 hr under inert atmosphere and azeotropic water removal (Dean-Stark). The $CHCl_3$ and excess of o-aminophenol was evaporated under reduced pressure, and the crude product **18** was identified by the following spectroscopic data: NMR: ($CDCl_3$) δ (ppm) = 0.74 + 0.78 (s 3H, 18-CH_3), 1.07 [d (J = 6 Hz), 21-CH_3], 1.16 (s 19-CH_3), 5.69 (s 1H, H-4), 6.35 (b 1H, -OH), 6.57–7.2 (m 4H, Arom.), 7.84 + 7.94 [d (J = 2 Hz) + b s 1H, aldiminic H]. IR: (neat) 3380 (-OH), 1685 (-C=N), 1660–1650 (broad), 1605 cm^{-1}.

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Arch. Pharm. (Weinheim) *312*, 198–205 (1979)

Beiträge zum Studium einiger Heterocyclen, 49. Mitt.

Darstellung und Konfigurationsbestimmung der Oxime von 2-Benzyl-4-acetyl-5-Y-thiazolen und 2-Benzoyl-4-methoxycarbonyl-5-Y-thiazolen

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Eingegangen am 23. März 1978

Es wird die Darstellung von 2-Benzyl-4-acetyl-5-Y-thiazolen und 2-Benzoyl-4-methylcarbonyl-5-Y-thiazolen untersucht. Bei Behandlung mit Hydroxylamin wird im Falle der ersten Verbindungen ein einziges Oxim erhalten, dessen Konfiguration ein Anti-thiazol ist. Im Falle der zweiten Verbindungsgruppe werden zwei isomere Oxime in verschiedenen Mengenverhältnissen erhalten. Die Struktur der Verbindungen wurde mit Hilfe der Beckmann-Umlagerung und der Massenspektren ermittelt.

0365-6233/79/0303-0198 $ 02.50/0