105–129 c.p.s. (m, 10.0), 205–224 c.p.s. (m, 6.0), 284 c.p.s. (b, 1.8), 420–466 c.p.s. (m, 20.4).

Anal. Calcd. for $C_{32}H_{38}N_4$: C, 80.29; H, 8.00; N, 11.71. Found: C, 80.42; H, 7.93; N, 11.58.

Reduction of bis-Derivative 3b

This reaction was effected essentially as described above for **2c** to give, after recrystallization from methanol–acetonitrile, 1.60 g (61%) of hydrazine **5** (tan crystals), m.p. 126–127°; i.r. 3440 cm^{-1} (NH), 1603 and 1505 cm^{-1} (aromatic), 1270 and 1315 cm^{-1} (C—N), 765 and 690 cm^{-1} (out-of-plane CH bend); n.m.r. ($CDCl_3$) 124 c.p.s. (d, 6.0, $J = 9$), 215 c.p.s. (qt, 2.0, $J = 9$), 290 c.p.s. (s, 4.1), 355 c.p.s. (b, 2.1), 432–476 c.p.s. (m, 24.0).

Anal. Calcd. for $C_{36}H_{38}N_4$: C, 82.09; H, 7.27; N, 10.64. Found: C, 81.91; H, 7.32; N, 10.39.

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Steroid derivatives of cysteamine and cysteine

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A number of androstenone, estrone, and pregnenone derivatives of cysteamine have been prepared by reacting the steroid amines with ethylene monothiolcarbonate. The amides of androstenone carboxylic acid with mercaptoethylamine and cysteine have also been prepared.

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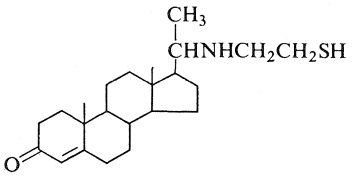
The only compounds which have shown any promise in affording protection against radiation in the animal body are cysteamine (2-mercaptoethylamine) and its simple derivatives (1). Cysteine, which was one of the first compounds reported to show radiation protection, is less effective (2). However, these compounds are relatively toxic and are also easily metabolized and eliminated from the body. The object of this work was to prepare derivatives which might be less toxic and less readily metabolized, by joining cysteamine and cysteine to a steroid molecule, while still leaving the mercapto group free, since this is essential for radiation protection. The following derivatives of cysteamine have been prepared: *N*-(2-mercaptoethyl)-3-ketopregn-4-en-20β-yl amine (**1**), *N*-(2-mercaptoethyl)-3-keto-androst-4-en-17β-yl amine (**2**), *N*-(2-mercaptoethyl)estra-1,3,5(10)-trien-3-ol-17β-yl amine (**3**), and *N*-(2-mercaptoethyl)-3-ketoandrost-4-ene 17β-carboxamide (**4**). A derivative of cysteine, *N*-(3-ketoandrost-4-ene 17β-carboxyl)cysteine (**5**), has also been synthesized.

The condensation of pregn-5-en-3-ol-20-amine with an excess of ethylene monothiolcarbonate gave a good yield of *N*-mercaptoethylpregn-5-en-3-ol-20β-yl amine. Although condensations with ethylene monothiolcarbonate are usually carried out (3, 4) with an excess of amine to avoid di-substitution, no *N,N*-dimercaptoethyl derivative was formed in the present case. This same compound was formed by using one equivalent of ethyl 2-mercaptoethylcarbonate (4). An Oppenauer oxidation of *N*-(2-mercaptoethyl)pregn-5-en-3-ol-20-yl amine under standard conditions gave *N*-(2-mercaptoethyl)-3-ketopregn-4-en-20β-yl amine (**1**), without oxidizing the mercapto group, although the yield was low. The molecular weight indicated that the compound was still in the free mercapto form.

As an alternative route pregn-5-en-3-ol-20β-yl amine was oxidized with chromium trioxide in pyridine (5) to 3-ketopregn-5-en-20β-yl amine, which was obtained in an impure state and in low yield, apparently due to the formation of chromium complexes. Oxidation of the corre-



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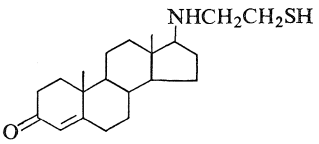

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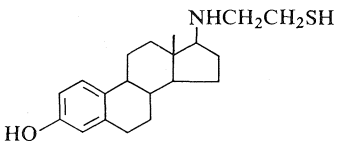

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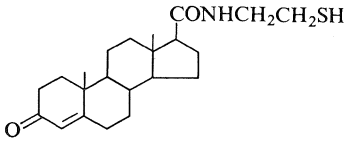

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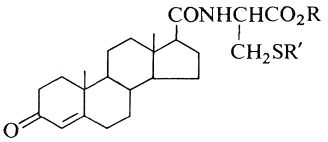

5 *a*; R = R′ = H
b; R = CH_3, R′ = $PhCH_2$

sponding amine hydrochloride following the method of Jones (6) gave only traces of the keto-amine. 3-Ketopregn-5-en-20β-yl amine could not be isomerized to 3-ketopregn-4-en-20β-yl amine with oxalic acid (7), but isomerization was achieved with alcoholic potassium hydroxide at room temperature.

Androst-5-en-3-ol-17β-yl amine also condensed with ethylene monothiolcarbonate to give *N*-(2-mercaptoethyl)androst-5-en-3-ol-17β-yl amine, which was oxidized under the conditions of Oppenauer to *N*-(2-mercaptoethyl)-3-ketoandrost-4-en-17β-yl amine (**2**). Estra-1,3,5(10)-trien-3-ol-17β-yl amine also reacted readily with ethylene monothiolcarbonate to give *N*-(2-mercaptoethyl)estra-1,3,5(10)-trien-3-ol-17β-yl amine (**3**).

3-Ketoandrost-4-ene 17β-carboxylic acid was converted to its acid chloride with oxalyl chloride and condensed with mercaptoethylamine to give *N*-(2-mercaptoethyl)-3-ketoandrost-4-ene 17β-carboxamide (**4**). The acid chloride was also reacted with cysteine in the presence of triethylamine to form *N*-(3-ketoandrost-4-ene 17β-carboxyl)cysteine (**5***a*). Condensation could not be effected in the presence of pyridine. Previously the acid chloride had been condensed with *S*-benzylcysteine methyl ester to afford *S*-benzyl-*N*-(3-ketoandrost-4-ene 17β-carboxyl)cysteine methyl ester (**5***b*). However, since the free cysteine derivative was prepared by direct condensation, hydrolysis and debenzylation of this last compound were not attempted.

Experimental

Analyses were performed by Dr. Jansen, Beerse, Belgium.

Pregn-5-en-3-ol-20β-yl Amine

Pregnenolone oxime (lit. (8) m.p. 218–219°) was reduced with sodium in *n*-propanol (9) to the amine hydrochloride, m.p. 304–305°. The free base was liberated with 30% aqueous sodium hydroxide, m.p. 165–167° (lit. (9) m.p. 163–166°).

N-(2-Mercaptoethyl)pregn-5-en-ol-20β-yl Amine

Pregn-5-en-3-ol-20β-yl amine (1.0 g) was dissolved in toluene (50 ml) and the solution dried by distilling off half the solvent. Ethylene monothiolcarbonate (0.165 g) was then added and the mixture refluxed for 15 h. Part of the solvent was evaporated at reduced pressure, when the product (0.97 g) crystallized and was then recrystallized from acetone, m.p. 152–154°.

As an alternative method, pregn-5-en-3-ol-20β-yl amine (0.765 g) in dry toluene (25 ml) was treated over 1 h at reflux with ethyl 2-mercaptoethylcarbonate (0.362 g) (4). The solution was refluxed for ½ h and the solvent removed *in vacuo*. The product (0.65 g) was recrystallized from acetone to m.p. 152–154°.

Anal. Calcd. for $C_{23}H_{39}NOS$: C, 73.25; H, 10.41. Found: C, 73.69; H, 10.60.

N-(2-Mercaptoethyl)-3-ketopregn-4-en-20β-yl Amine (1)

The above compound (0.55 g) was dissolved in toluene (200 ml) and cyclohexanone (30 ml). Part (70 ml) of the solvent was distilled off and aluminium isopropoxide (4.0 g) in toluene (30 ml) added dropwise while the solvent

(50 ml) was distilled off. The mixture was refluxed for 15 h, Rochelle salt (5 g) was then added and the mixture steam distilled. The product was extracted from the residue with ether and recrystallized from acetone – petroleum ether (0.23 g) m.p. 186–188° (decomp.); λ_{max} 242 mμ (log ε 4.03).

Anal. Calcd. for $C_{23}H_{37}NOS$ (mol. wt., 373): C, 73.54; H, 9.93. Found (mol. wt. (Rast), 363): C, 73.35; H, 9.71.

Androst-5-en-3-ol-17β-yl Amine

Phosphorus oxychloride (1.0 ml) was added dropwise to pregnenolone oxime (0.5 g) in pyridine (7.0 ml) with stirring and cooling to 0°. The mixture was maintained at 0–5° for 1½ h and then poured into ice and dilute hydrochloric acid. The acetylamino compound was filtered off, washed with water and recrystallized from methanol water, m.p. 245–247°. The hydrolysis was carried out by refluxing overnight with 20% potassium hydroxide in ethylene glycol. The product was extracted with ether and the amine hydrochlorides (0.2 g); m.p. 362° (lit. (10) m.p. 360°) precipitated by passing in hydrogen chloride. The free amine was liberated with 30% sodium hydroxide and recrystallized from acetone (0.11 g), m.p. 161–164° (lit. (10) m.p. 162°).

N-(2-Mercaptoethyl)androst-5-en-3-ol-17β-yl Amine

Androst-5-en-3-ol-17β-yl amine was condensed as above with ethylene monothiolcarbonate. The product, m.p. 150–152°, was recrystallized from acetone.

Anal. Calcd. for $C_{21}H_{35}NOS$: C, 72.15; H, 10.09. Found: C, 72.41; H, 9.93.

N-(2-Mercaptoethyl)-3-ketoandrost-4-en-17β-yl Amine (2)

N-Mercaptoethylandrost-5-en-3-ol-17β-yl amine (0.72 g) was subjected to an Oppenauer oxidation as before giving the product (0.31 g), m.p. 193–196° (decomp.), from acetone – petroleum ether; λ_{max} 241 mμ (log ε 4.02).

Anal. Calcd. for $C_{21}H_{33}NOS$ (mol. wt., 348): C, 72.57; H, 9.57. Found (mol. wt. (Rast), 343): C, 72.83; H, 9.82.

Estra-1,3,5(10)-trien-3-ol-17β-yl Amine

Estrone oxime (0.8 g) (m.p. 231–232°) (11) in *n*-propanol (50 ml) was refluxed with small pieces of sodium (1.48 g) until they dissolved. The solvent was evaporated at reduced pressure, water added, and carbon dioxide passed in. The precipitated solid was washed with hot water and recrystallized from methanol (0.3 g), m.p. 223–226° (lit. (11) m.p. 222–223°).

N-(2-Mercaptoethyl)estra-1,3,5(10)-trien-3-ol-17β-yl Amine (3)

Estratriene-3-ol-17β-yl amine (0.237 g) and ethylene monothiolcarbonate (0.041 g) in toluene (1.3 ml) under the usual conditions, gave mixed crystals (0.18 g) of the estratriene-3-ol-17β-yl amine and *N*-(2-mercaptoethyl)-estratrien-3-ol-17β-yl amine, recrystallized from acetone, m.p. 129–130°.

Anal. Calcd. for $C_{20}H_{29}NOS \cdot C_{18}H_{25}NO$: C, 75.70; H, 9.03. Found: C, 75.78; H, 8.97.

N-(2-Mercaptoethyl)-3-ketoandrost-4-ene 17β-carboxamide (4)

3-Ketoandrost-4-ene 17β-carboxylic acid (1.0 g) prepared by hypobromite oxidation of progesterone (12), was dissolved in 0.79 *N* sodium hydroxide (39 ml). The water was evaporated and the sodium salt dried at 170° and 1 mm for 5 h. The salt was suspended in anhydrous pyridine (0.16 g) and benzene (15 ml), cooled to 5°, and treated with oxalyl chloride (4.5 ml). The mixture was allowed to stand at room temperature for 5 min and evaporated *in vacuo* at 20°. Benzene (2 ml) was added and the solution reevaporated. The residue was dissolved in benzene (12 ml), cooled to 0°, and a suspension of freshly sublimed mercaptoethylamine (0.24 g) in benzene (5 ml) added with stirring. The solution was left at room temperature overnight and then evaporated. The residue was triturated with 10% sodium carbonate. The remaining solid was recrystallized from acetone–ether to crystals (0.66 g), m.p. 148–150° (decomp.); λ_{max} 242 mμ (log ε 4.08).

Anal. Calcd. $C_{22}H_{31}NO_2S \cdot H_2O$: C, 67.14; H, 8.96. Found: C, 67.33; H, 8.08.

N-(3-Ketoandrost-4-ene 17β-carboxyl)cysteine (5a)

3-Ketoandrost-4-ene 17β-carboxylic acid (0.33 g) was converted as above to its acid chloride, and this in benzene (4 ml) added dropwise at 0° with stirring to a solution of cysteine hydrochloride (0.16 g) in triethylamine (0.15 ml) and tetrahydrofuran (5 ml). A further amount of triethylamine (0.15 ml) was added during the addition. The reaction was stirred overnight, and then poured into water (10 ml) and acidified with a few drops of hydrochloric acid. The product was recovered by ether extraction, and recrystallized from acetone–hexane, m.p. 175–180° (decomp.); λ_{max} 242 mμ (log ε 4.10).

Anal. Calcd. for $C_{23}H_{33}NOS$: C, 65.84; H, 7.92. Found: C, 65.92; H, 7.68.

S-Benzyl-N-(3-ketoandrost-4-ene 17β-carboxyl)cysteine Methyl Ester (5b)

3-Ketoandrost-4-ene 17β-carboxylic acid (0.33 g) was converted to the acid chloride and added to *S*-benzyl-L-cysteine methyl ester (0.24 g (13)), m.p. 147°, and triethylamine (0.15 ml) in benzene (5 ml) cooled to 10°. Evaporation of the solvent and trituration with ether gave the product, m.p. 115–117°.

Anal. Calcd. for $C_{31}H_{41}NO_4S$: C, 71.09; H, 7.89. Found: C, 70.93; H, 7.75.

Acknowledgment

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Convenient *C*-alkylation of some acyloins

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Acetoin, adipoin, and benzoin are conveniently alkylated by benzyl chloride and methyl iodide in 1,2-dimethoxyethane solution using sodium hydride as the base. Only alkylation at carbon is observed. Little or no alkylation occurs at oxygen.

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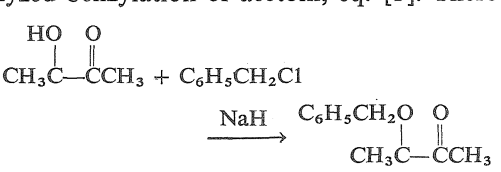
A large quantity of 3-benzyloxy-2-butanone was required in these laboratories. A possible route to this compound appeared to be the base-catalyzed benzylation of acetoin, eq. [1]. There



[1] $CH_3C(HO)(C{=}O)CH_3 + C_6H_5CH_2Cl \xrightarrow{NaH} CH_3C(C_6H_5CH_2O)(C{=}O)CH_3$

appear to be few studies of base-catalyzed alkylations of acyloins. There are a number of reports of alkylation at oxygen in reactions between dianions of enediols and alkyl halides (1–4). However, alkylation at carbon has also been observed in such systems (5, 6), and appears to be general in simple cases (6). Also, acyloins give products of reaction at carbon in the base-catalyzed aldol (7) and Michael (8–10) condensation reactions with aldehydes and activated olefins, respectively, presumably via the monoanion.

A convenient procedure for the methylation of alcohols (11, 12) was adapted for the benzylation of acetoin. Addition of sodium hydride in small portions to a 1,2-dimethoxyethane solution of equimolar amounts of acetoin and benzyl chloride at room temperature resulted in a rapid reaction. The product, isolated in 45% yield, did not have spectral properties expected for 3-benzyloxy-2-butanone. The infrared spectrum (CCl_4) showed strong hydroxyl absorption at 3480 cm^{-1}. No absorptions characteristic of the CH_3—CH— group could be detected in the nuclear magnetic resonance (n.m.r.) spectrum. The material was identified as 3-benzyl-3-hydroxy-2-butanone on the basis of its n.m.r. spectrum, taken in carbon tetrachloride, which showed singlet absorptions at τ 2.86 (5.0 H) for the phenyl protons, τ 6.15 (0.93 H) for the hydroxyl proton, τ 7.13 (1.85 H) for the methylene protons, and at τ 7.95 (2.84 H) and τ 8.76 (3.24 H) for the protons of the two methyl groups. Alkylation had thus occurred at the carbon atom and there was no evidence for any product resulting from alkylation at oxygen.

A brief extension of the alkylation of acyloins was made, using the same procedure, to include methylation and benzylation of acetoin, benzoin, and adipoin. Yields of alkylated products ranged from 40% to 70%. Alkylation at the ketol carbon appeared to be the exclusive reaction in all cases except in the methylation of adipoin. In this case the presence of a singlet at τ 6.9 in the n.m.r. spectrum (CCl_4) of the crude product indicates that some *O*-alkylation might have occurred. However, the major product resulted from carbon alkylation. In the other cases no n.m.r. spectral evidence was found for the formation of any *O*-alkylated materials.

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