

hexanenitrile¹ with Adam's catalyst in the presence of acetic anhydride gave the desired compound in 58% yield as a red, viscous liquid, bp 173° (0.5 mm), n_D^{25} 1.4679. *Anal.* (C₈H₁₆N₂O₄) C, H, N. Nef hydrolysis of this 4-nitro compound gave the previously unreported 4-ketohexanenitrile, bp 75–80° (0.5 mm), n_D^{20} 1.4338. *Anal.* (C₆H₁₀NO) C, H, N.

(4) G. D. Buckley, T. J. Elliott, F. G. Hunt, and A. Loebe, *J. Org. Chem.*, **8**, 10 (1943).

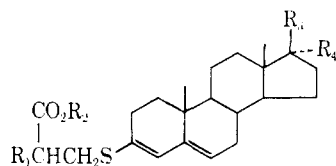
Cysteine Derivatives of Keto Steroids

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The condensation of L-cysteine derivatives with Δ^4 -3-keto steroids in the presence of pyridinium chloride¹ has been found to give the corresponding diene thioethers.² When compared with testosterone in mice, **3** was devoid of androgenic, myotropic, and antiestrogenic activity.³



- 1**, R₁ = C₆H₅CH₂CONH; R₂ = CH₃; R₃ = C₈H₁₇; R₄ = H
2, R₁ = Cl-H₃N⁺; R₂ = C₂H₅; R₃ = OH; R₄ = H
3, R₁ = Cl-H₃N⁺; R₂ = C₂H₅; R₃ = OH; R₄ = CH₃

Experimental Section⁴

Methyl S-(3,5-Cholestadien-3-yl)-N-phenylacetyl-L-cysteinate (1).—A solution of 500 mg (1.3 mmoles) of cholestone in 25 ml of C₆H₆ was distilled until 5 ml had collected. A solution composed of 880 mg (5.2 mmoles) of methyl N-phenylacetyl-L-cysteinate,⁵ 48 mg of pyridinium chloride, 6 ml of EtOH, and 4 ml of C₆H₆ was added. The solution was refluxed 3 hr, cooled, diluted with 30 ml of ether, and washed with two 25-ml portions of 1 N NaOH. After one H₂O wash the ethereal solution was dried (Na₂SO₄) and evaporated leaving 740 mg of semisolid. Precipitation from acetone-petroleum ether (bp 30–60°) gave 264 mg of **1**, mp 119–125°. Further work-up of the mother liquor gave another 100 mg of **1**, mp 100–119°, and 167 mg of recovered cholestone. The analytical sample (*i*-Pr₂O) had mp 158–159°. *Anal.* (C₃₉H₅₇NO₈S) H, N, S.

Ethyl S-(17 β -Hydroxy-3,5-androstadien-3-yl)-L-cysteinate Hydrochloride (2).—A similar condensation between testosterone and ethyl L-cysteinate hydrochloride gave **2** as an amorphous solid (acetone), mp 176–179°. *Anal.* (C₂₇H₄₅ClNO₆S) C, H, Cl, N, S.

Ethyl S-(17 β -Hydroxy-17 α -methyl-3,5-androstadien-3-yl)-L-cysteinate Hydrochloride (3).—Similarly, 17 α -methyltestosterone and ethyl L-cysteinate hydrochloride gave **3**, needles (Me₂CO-C₆H₆), mp 171–172°. *Anal.* (C₂₈H₄₆ClNO₆S) C, H, Cl, N, S.

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(1) J. Roma, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(2) Δ^4 -3-Keto steroids are reported not to react with cysteine or ethyl cysteinate: S. Lieberman, *Experientia*, **2**, 411 (1945).

(3) We are indebted to Dr. R. Kraay, Eli Lilly and Co., for these assays.

(4) Ir spectra were obtained on an Infracord, uv spectra on a Beckman DU. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(5) Z. Foldi, *Acta Chim. Acad. Sci. Hung.*, **5**, 187 (1954); *Chem. Abstr.*, **50**, 981i (1956).

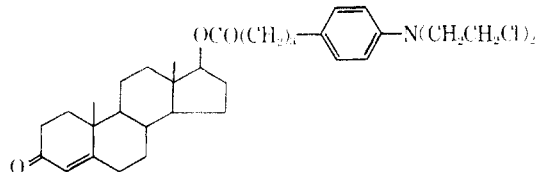
17 β -(4'-[p-[Bis(β -chloroethyl)amino]phenyl]-butanoyloxy)-4-androsten-3-one

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The synthesis and antitumor evaluation of steroidal nitrogen mustards¹ prompted us to synthesize the chlorambucil ester of testosterone by treating chlorambucil chloride with the potassium salt of testosterone in refluxing benzene.



Experimental Section²

17 β -(4'-[p-[Bis(β -chloroethyl)amino]phenyl]-butanoyloxy)-4-androsten-3-one.³—Testosterone, 0.34 g (1.1 mmoles), was dissolved in dry C₆H₆, excess K was added, and the mixture was then refluxed overnight. After filtration of the unreacted K, the C₆H₆ solution of the potassium salt was added to residual chlorambucil chloride, which was prepared from 0.35 g (1.1 mmoles) of chlorambucil and 2 ml of POCl₃ in refluxing C₆H₆ with subsequent solvent removal. The esterification reaction mixture was refluxed 5 hr, then left at room temperature overnight. The solvent was evaporated to give 512 mg of crude product, which was chromatographed on 10 g of Al₂O₃. C₆H₆ eluted 60 mg of acid chloride, 43 mg of the ester (analytical sample), and 34 mg of impure ester, while C₆H₆-Et₂O (4:1) eluted 154 mg of additional ester. Rechromatography of the last two fractions (188 mg) plus 82 mg of similar product from another preparation on 8 g of Al₂O₃ gave 211 mg of ester eluted by C₆H₆-Et₂O (4:1). *Anal.* (C₃₈H₅₅Cl₂NO₃) C, H, N.

(1) (a) G. V. Rao and C. C. Price, *J. Org. Chem.*, **27**, 205 (1962); (b) S. H. Barshein and R. J. Ringold, *ibid.*, **26**, 3084 (1961); (c) W. J. Gensler and G. M. Sherman, *ibid.*, **23**, 1227 (1958); (d) A. M. Kilaetskii, M. V. Vasil'eva, and E. M. Balquova, *Sovetsk. Produkty iz Ksoifoli i Skipidato. Abstr. Nauch. Belorussk. SSR, Tsent. Nauch.-Issled. i Proekt. Inst. Lesokhim. Prom., Te. Tses. Nauch.-Tekhn. Sposobch., Gochi*, 227 (1964); *Chem. Abstr.*, **62**, 9194 (1965); (e) G. R. Vasasour, H. I. Bolker, and A. F. McKay, *Can. J. Chem.*, **30**, 933 (1952); (f) R. E. Havranek and N. J. Dourenbos, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 328 (1960); (g) T. Nogrady, K. M. Vagi, and V. W. Adamkiewicz, *Can. J. Chem.*, **40**, 212B (1962); (h) L. N. Volovelskii and A. B. Simkina, *Zh. Obshch. Khim.*, **37**, 1571 (1967); (i) Nielsen-Duvaz, A. Combanis, and E. Tarnagocanu, *J. Med. Chem.*, **10**, 172 (1967); (j) C. R. Waik, T. C. Chou, and H. H. Liu, *ibid.*, **10**, 255 (1967).

(2) Ir spectra were obtained on an Infracord, uv spectra on a Beckman DU. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(3) This compound was submitted to the Cancer Chemotherapy National Service Center, Public Health Service, for an evaluation of its antitumor activity against acute lymphocytic leukemia.

2,2'-Hydrazobis(5-nitropyrimidines)

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2-Amino-5-nitropyrimidine and its derivatives possess pronounced trichomonocidal activity.¹ We have shown that symmetrical 2,2'-hydrazobis(5-nitrothiazoles) also show a very strong antiprotozoal activity.² The combination of these two features

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(2) M. Avramoff, S. Adler, and A. Fonner, *J. Med. Chem.*, **10**, 1138 (1967).