Steroidal Heterocycles: 2′-Thiocyanatoandrosteno-[3,2-*d*]pyrimidines and -[17,16-*d*]pyrimidines

By **Joginder S. Bajwa** and **Peter J. Sykes,*** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

The preparation of steroidal heterocycles containing the 2′-thiocyanatopyrimidine ring fused to the 2,3-position or 16,17-position of the steroid nucleus is described. These are prepared by the reaction of 2-amino-1,3,4-thiadiazole with 2-hydroxymethylene-3-oxo-steroids and 16-hydroxymethylene-17-oxo-steroids.

It was of interest to prepare fused steroidal pyrimidines since other heterocyclic fused steroids have been shown to exhibit modified or accentuated hormonal activities.[1] Various pyrimidine bases in the steroid series have already been obtained by reactions involving the condensation of 2-hydroxymethylene-3-oxo-steroids with guanidine, urea, and thiourea [2] or by the treatment of ketones with trisformylaminomethane [3] and cyanoguanidine.[4] 2α-Cyano-3-oxo-steroids and their enol ethers have also been used as starting materials for the preparation of pyrimidine bases.[2] This paper describes another convenient synthesis of some androsteno-[3,2-*d*]pyrimidines and androsteno[17,16-*d*]pyrimidines by the reaction of 2-amino-1,3,4-thiadiazole (1) with steroidal β-diketones.

The condensation of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (2) with 2-amino-1,3,4-thiadiazole (1) in refluxing toluene in the presence of a catalytic amount of toluene-*p*-sulphonic acid gave 17β-hydroxy-2′-thiocyanato-5α-androst-2-eno[3,2-*d*]pyrimidine (4) in 60% yield. The i.r. spectrum of this compound exhibited a strong band at 2 160 cm^{-1} indicative of a thiocyanate group and also bands at 1 565, 1 555infl, 1 545infl, 1 415, 1 365, and 755 cm^{-1} characteristic of a pyrimidine ring. The ^1H n.m.r. spectrum showed a singlet at δ 8.25 confirming the 6′-hydrogen of the pyrimidine ring.

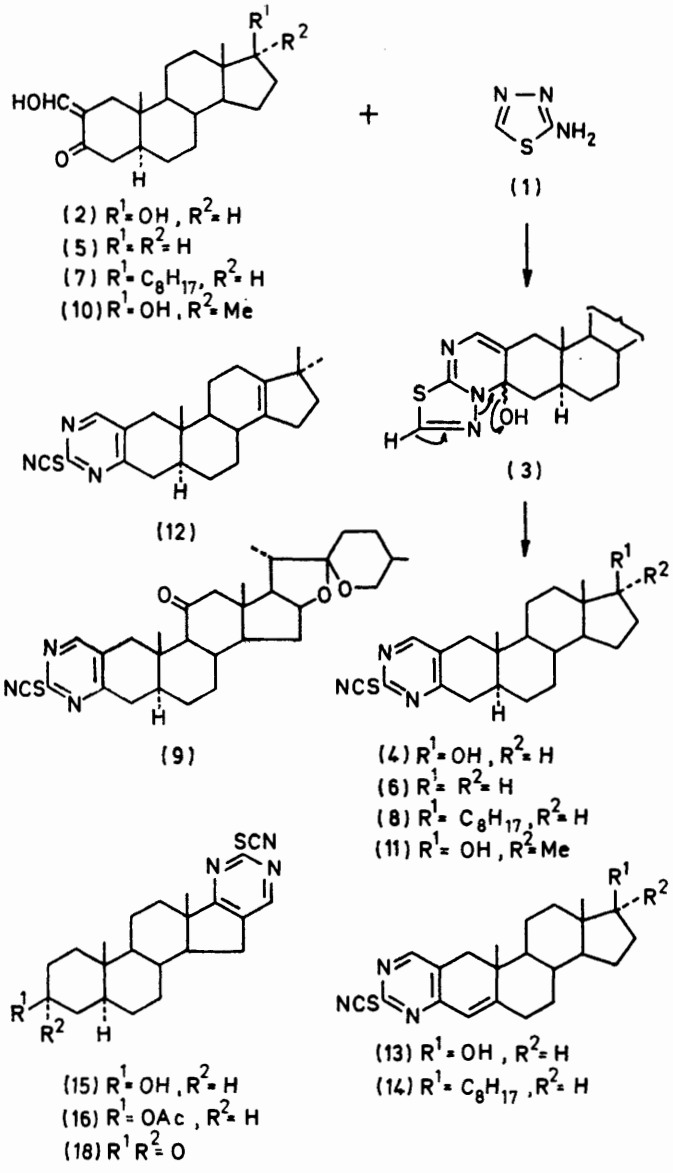
It is apparent that the final dehydration of the initial condensation product (3) results in a rearrangement furnishing the thiocyanato-pyrimidine ring system. Indeed a similar rearrangement has been reported [5] during the reaction between 2-amino-1,3,4-thiadiazole and the simple 1,3-dicarbonyl compound, acetylacetone, resulting in the formation of 2-thiocyanato-4,6-dimethylpyrimidine.

The intermediate condensation product (3) could not be isolated and it is, therefore, possible that it might have an isomeric structure based upon an initial reaction between the amino-group of (1) and the 3-carbonyl group of the steroid. However fission of the N–N bond in the dehydration step of either of the possible intermediates will yield the same product.

The thiocyanate group is known to isomerise to the isothiocyanate structure on refluxing in acetonitrile,

[1] R. E. Counsell and P. D. Klimstra, 'Medicinal Chemistry,' ed. by A. Burger, Wiley–Interscience, New York, 1970, 3rd edn., Part II, p. 923.
[2] P. de Ruggieri, C. Landolfi, and D. Chiaramonti, *Gazzetta*, 1962, **92**, 768.
[3] H. Bredereck, R. Gompper, and B. Geiger, *Ber.*, 1960, **93**, 1402.
[4] L. L. Smith, D. M. Teller, and T. H. Foell, *J. Medicin. Chem.*, 1963, **6**, 330.
[5] R. F. Lauer and G. Zenchoff, *J. Heterocyclic Chem.*, 1976, **13**, 291.

benzene, and toluene.[6] However, no such isomerisation was observed in the above synthesis, the 2′-thiocyanate



group remaining intact even after prolonged heating in refluxing xylene. Absence of isomerisation to isothiocyanate was confirmed in that the product failed to react with a primary amine.

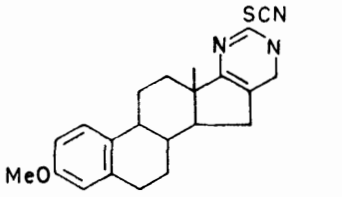
In a similar manner 2′-thiocyanato-5α-androst-2-eno-[3,2-*d*]pyrimidine (6), 2′-thiocyanato-5α-cholest-2-eno-[3,2-*d*]pyrimidine (8), and 11-oxo-2′-thiocyanato-5α-spirostan-2-eno[3,2-*d*]pyrimidine (9) were prepared from the corresponding 2-hydroxymethylene-3-oxo-steroids (5), (7), and 2-hydroxymethylene-5α-spirostane-3,11-dione respectively.

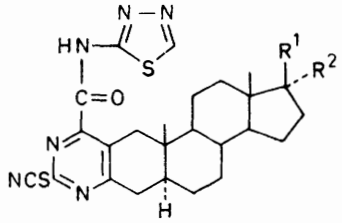
Using the reaction conditions necessary for the condensation reaction, a 2-hydroxymethylene-3-oxo-steroid having a tertiary hydroxy-group at C-17, also undergoes a Wagner–Meerwein rearrangement. For example, 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (10) gave the expected 2′-thiocyanatopyrimidine (11) accompanied by a variable amount of 17,17-dimethyl-2′-thiocyanato-18-norandrost-2,13-dieno-[3,2-*d*]pyrimidine (12) depending upon the quantity of toluene-*p*-sulphonic acid used in the reaction.

The reaction was also successfully applied to two steroids with a Δ^4-double bond, namely 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one and 2-hydroxymethylenecholest-4-en-3-one, but the yields of the products, 17β-hydroxy-2′-thiocyanatoandrost-2,4-dieno-[3,2-*d*]pyrimidine (13) and 2′-thiocyanatocholest-2,4-dieno[3,2-*d*]pyrimidine (14) were lower, being in the range 35—40%. Analogously fused 3β-hydroxy-2′-thiocyanato-5α-androst-16-eno[17,16-*d*]pyrimidine (15), and 3-methoxy-2′-thiocyanato-oestra-1,3,5(10),16-tetraeno[17,16-*d*]pyrimidine (17) were prepared from 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one and 16-hydroxy-methylene-3-methoxyoestra-1,3,5(10)-trien-17-one respectively. Acetylation of the 3-hydroxysteroid (15) gave the corresponding acetyl derivative (16) whilst oxidation by Jones reagent furnished the 3-oxo derivative (18).

The reaction of 17β-hydroxy-2-ethoxycarbonyl-(hydroxy)methylene-17α-methyl-5α-androstan-3-one with (1) under the same conditions furnished the expected 17β-hydroxy-17α-methyl-6′-(1,3,4-thiadiazol-2-ylcarbamoyl)-2′-thiocyanato-5α-androst-2-eno[3,2-*d*]-pyrimidine (19). A further example of this reaction was illustrated by the conversion of 2-ethoxycarbonyl-(hydroxy)methylene-5α-cholestan-3-one into 6′-(1,3,4-thiadiazol-2-ylcarbamoyl)-2′-thiocyanato-5α-cholest-2-eno[3,2-*d*]pyrimidine (20).

Under the same reaction conditions 2α-acetyl-17β-hydroxy-5α-androstan-3-one failed to yield any con-





densation product, probably because ketones, in this case the 2α-acetyl group, generally react with amines

[6] U. Tonellato, O. Rossetto, and A. Fava, *J. Org. Chem.*, 1969, **34**, 4032.

much more slowly than aldehydes (the 2-formyl group) to yield Schiff's bases.[7]

EXPERIMENTAL SECTION

M.p.s were determined on Gallenkamp apparatus and are uncorrected. I.r. spectra were recorded in bromoform on a Perkin–Elmer 157 G Spectrometer. ^{1}H N.m.r. spectra were recorded in deuteriated chloroform using tetramethylsilane as an internal standard on a Nuclear Magnetic Resonance Ltd EM360 (60 MHz) or a Varian HA 100 (100 MHz) spectrometer. Mass spectrometry was carried out on AEI MS 902 instrument.

All the starting materials except 2-hydroxymethylene-5α-spirostane-3,11-dione, which has not been reported so far, were prepared by the known literature methods.

2-Hydroxymethylene-5α-spirostane-3,11-dione.— Sodium hydride (1.5 g) was added to a solution of 5α-androstane-3,11-dione (5 g) in benzene (100 ml) and ethyl formate (5 ml) and the reaction mixture was set aside under nitrogen for one day. Methanol (10 ml) was added to decompose the excess of sodium hydride and the solution was diluted with water (300 ml). The layers were separated and the basic solution was extracted with ether to remove the neutral material. The aqueous layer was then acidified with 3M-hydrochloric acid (40 ml) and the liberated enol extracted with ether. The ether layer was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to dryness. The crude product was recrystallised from ethanol to give *2-hydroxymethylene-5α-spirostane-3,11-dione* (3.5 g, 66%), m.p. 165—166. I.r. ($CHBr_3$) $\nu_{max.}$ 2 930, 2 870, 1 700 (C=O), 1 640, 1 585 (COC=CHOH), 1 450, 1 385, and 1 375 cm^{-1}; ^{1}H n.m.r. δ 0.72, 0.82, 0.95, 1.00 (methyl groups), and 8.60 (s, 1 H, 2=CHO) (Found: C, 73.20; H, 8.91. Calc. for $C_{28}H_{40}O_5$: C, 73.68; H, 8.77%).

General Procedure for the Condensation Reaction.—A solution of steroidal β-diketone (0.001 mol), 2-amino-1,3,4-thiadiazole (0.0015 mol), and toluene-*p*-sulphonic acid (20 mg) in dry toluene (50 ml) was refluxed and stirred overnight. The reaction mixture was cooled and the solvent was removed under reduced pressure to leave a residue which was chromatographed over silica gel (50 g; 80—200 mesh) using either methylene chloride or methylene chloride–ethanol (95 : 5). A summary of results is given in the Table. Compounds (4) and (6) were recrystallised from benzene and acetone respectively whilst all other products were recrystallised from ethanol.

17β-Hydroxy-17α-methyl-2′-thiocyanato-5α-androst-2-eno[3,2-d]*-pyrimidine* (11) and *17,17-Dimethyl-2′-thiocyanato-18-norandrost-2,13-dieno*[3,2-d]*pyrimidine* (12).—The crude product from the condensation reaction was chromatographed over silica gel. Elution with methylene chloride gave the rearranged steroid (12) which was recrystallised from ethanol whilst further elution with methylene chloride–ethanol (95 : 5) mixture gave the expected condensation product (11) which was recrystallised from ethanol.

[8/506 *Received*, 20*th March*, 1978]

[7] R. W. Hayes, *Chem. Rev.*, 1963, **63**, 489.

Compd.	Mol. Formula	Yield (%)	M.p. (°C)	High resolution mass spectrum Found	Calculated	Characteristic i.r. abs (ν/cm^{-1})	^{1}H N.m.r. (δ) 6′-H	18-CH_3	19-CH_3	Analysis Found (%) C	H	N	Calculated (%) C	H	N
(4) *b*	$C_{32}H_{49}N_3OS$	60	213—215	383.202 537	383.203 123	2 160 (SCN), 1 565, 755	8.20	0.75	0.75	69.0	7.6	11.1	68.89	7.63	10.96
(6) *a*	$C_{32}H_{49}N_3S$	85	210—212	367.205 933	367.207 136	2 160 (SCN), 1 565, 755	8.30	0.70	0.75	71.7	8.0	11.65	71.89	7.96	11.44
(7) *a*	$C_{30}H_{45}N_3S$	70	159—160	479.331 357	479.333 404	2 160 (SCN), 1 565, 755	8.30			75.3	9.45	8.55	75.10	9.46	8.76
(9) *b*	$C_{30}H_{49}N_3SO_2$	68	241—243	521.271 406	521.271 198	2 160 (SCN), 1 695 (CO), 1 565, 755	8.30			68.75	7.95	8.1	69.06	7.54	8.08
(12) *a*	$C_{23}H_{29}N_3S$	11	125—127	379.208 494	379.308 209	2 160 (SCN), 1 565, 755	8.30	0.80 17-gem dimethyl	1.00	72.75	7.85	10.5	72.78	7.71	10.71
(13) *a*	$C_{32}H_{47}N_3SO$	41	185—187	381.186 086	381.187 474	2 160 (SCN), 1 620, 1 575, 750	8.20	0.80	1.00	68.75	7.25	10.8	68.25	7.13	11.02
(14) *a*	$C_{30}H_{43}N_3S$	38	184—186	477.316 335	477.317 754	2 160 (SCN), 1 620, 1 565, 770	8.20			75.25	8.9	8.5	75.42	9.08	8.80
(15) *b*	$C_{32}H_{49}N_3SO$	75	192—194	383.203 289	383.203 123	2 160 (SCN), 1 580, 790	8.35	0.85	0.97	69.1	7.75	10.95	68.89	7.63	10.96
(17) *b*	$C_{32}H_{49}N_3SO$	72	177—179	377.154 981	377.156 176	2 160 (SCN), 1 605, 1 575, 780	8.35	1.00		69.65	6.25	10.65	69.99	6.15	11.13
(18)	$C_{32}H_{47}N_3SO$	80	226—228	381.187 281	381.187 474	2 160 (SCN), 1 700 (CO), 1 575, 790	8.50	1.00	1.10	68.95	7.25	10.75	69.26	7.14	11.02
(16)	$C_{32}H_{51}N_3SO_2$	53	175—177	425.214 789	425.213 686	2 160 (SCN), 1 720 (CO), 1 580, 900	8.50	0.90	1.00	67.4	7.0	9.9	67.73	7.29	9.87
(19) *b*	$C_{36}H_{52}N_6S_2O_2$	65	244—246	524.204 927	524.202 805	3 330 (NH), 2 160 (SCN), 1 690 (CO), 1 510, 745	8.90 (5″-H), 12.0 (NH)	0.77	0.87 (1.20, 17-Me)	59.7	4.2	16.2	59.51	4.41	16.09
(20) *b*	$C_{63}H_{46}N_6S_2O$	71	311—314	606.317 398	606.317 434	3 330 (NH), 2 160 (SCN), 1 690 (CO), 1 500, 735	8.90 (5″-H) 12.00 (NH)			64.95	7.5	13.5	65.31	7.58	13.85
(11) *b*	$C_{33}H_{51}N_3SO$	85	172—173	397.218 722	397.218 773	2 160 (SCN), 1 565, 755	8.20	0.75	0.90 (1.20 17-Me)	69.5	7.85	10.95	69.48	7.86	10.57

a Methylene chloride was used for the elution of these compounds over silica gel. *b* Methylene chloride–ethanol (95 : 5) was used for elution of these compounds.