Conversion of Androst-5-ene-3β,17β-diol to Dehydroisoandrosterone on a Microgram Scale.—To 612 μg of [4-^{14}C]androst-5-ene-3β,17β-diol (47,000 cpm) was added 0.10 ml of dimethyl-*tert*-butylsilyl chloride solution which was prepared from 60 mg of dimethyl-*tert*-butylsilyl chloride and 70 mg of imidazole in 1.5 ml of DMF under cooling. The mixture was stored at 0° with occasional shaking. After 1 hr the reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4.

The 3-monosilyl ether purified by preparative tlc was oxidized with 0.2 ml of CrO_3–pyridine complex in 0.2 ml of pyridine at room temperature for 16 hr. Following usual work-up the oxidation product was treated without purification with 0.5 ml of a AcOH–H_2O–THF (3:1:1.5) solution at 55° for 3.5 hr. Ethanol was added and the solvent was evaporated under reduced pressure. The residue was submitted to tlc. The thin layer plate was scanned for radioactivity and the dehydroisoandrosterone area eluted was diluted with 20.2 mg of cold material and recrystallized to a constant specific activity of 335 cpm/μ*M* from acetone–hexane. Total counts were 23,800 cpm. This material was acetylated with Ac_2O and pyridine and the dehydroisoandrosterone acetate obtained was recrystallized to a constant specific activity of 334 cpm/μ*M* from aqueous acetone.

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Registry No.—I, 521-17-5; IIa, 42151-21-3; IIb, 42151-22-4; III, 42151-23-5; IV, 53-43-0; acetic acid, 64-19-7; tetra-*n*-butylammonium fluoride, 429-41-4; dimethyl-*tert*-butylsilyl chloride, 18162-48-6.

Heterocyclic Derivatives of Cholestane

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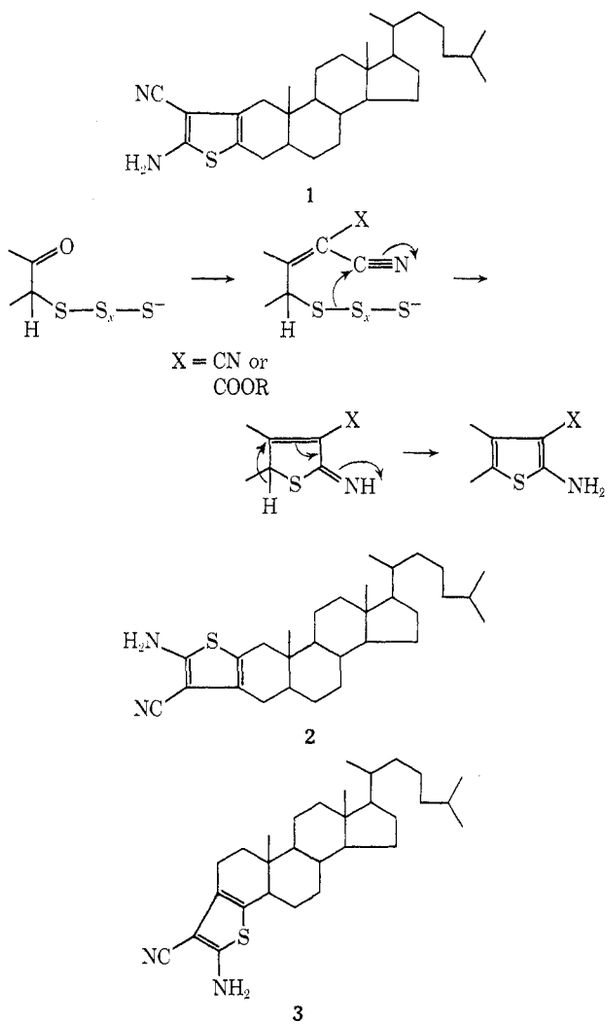
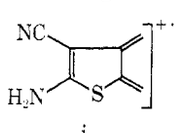
The reaction of cholestanone was reported[1] to give the 2′-aminocholest-2-eno[3,2-*b*]thiophene-4′-carbonitrile (**1**) under Gewalds'[2] conditions using sulfur and malononitrile. However, considering the proposed mechanism[2] (Scheme I) of the reaction, the assigned structure (**1**) seemed improbable. Since the initial step of the reaction requires enolization of the ketone followed by reaction with sulfur at the α position, the reaction product should have structure **2** as 3-keto steroids with 5α configuration are known[3] to enolize from the C_2 position to give the Δ^2 enol. However, the formation of the 4,3-*b* isomer (**3**) as a minor product of the reaction cannot be ruled out in view of the formation[4] of both the positional isomers of the steroidal indole derivatives from cholestanone by the Fischer indole synthesis. An unambiguous synthesis of **2** was achieved from cholestan-3-one-2α-thiol[5] following a known procedure.[6] The thiophene derivative (**2**) thus prepared was identical with the material prepared in our laboratory from cholestanone with sulfur and malononitrile.

Identical mass spectra of the samples of **2** from both

SCHEME I



the procedures indicate that the compound **2** obtained from cholestanone is free from the angular isomer **3**. The mass spectra of the compound **2** shows the peak for the molecular ion (*m/e* 466) besides a peak (*m/e* 150) for the retro-Diels–Alder fragment (i), which is the base



i

peak, with the metastable ion at *m/e* 48.5 (calcd, 48.3). Such a fragmentation is a characteristic mass spectral feature[7] of the steroidal heterocycles in which the heterocyclic ring is fused at the C_2 and C_3 positions of a Δ^2 steroid.

The melting point of the product **2**, prepared by both the procedures, is much higher than that reported[1,8] for the product obtained from cholestanone under Gewald's condition.

Since the preparation of pure alkanone-2-thiols, which are required for the regiospecific synthesis of the cycloalkenothiophene derivatives of type **2**, from the

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(2) K. Gewald, E. Schinke, and H. Bottcher, *Ber.*, **99**, 94 (1966).
(3) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, p 161.
(4) D. J. Harvey and S. T. Reid, *Tetrahedron*, **28**, 2489 (1972).
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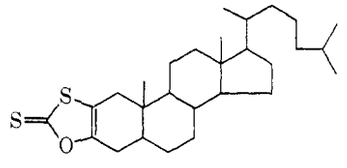
(7) H. E. Audier, J. Bottin, M. Fetizon, and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 4027 (1971); P. Jacquignon, M. Croisy-Delcey, and A. Croisy, *ibid.*, 4251 (1972); D. J. Harvey, W. A. Laurie, and R. I. Reed, *Org. Mass Spectrom.*, **5**, 1183 (1971).
(8) Professor Manhas has kindly informed the author that the actual melting point of **2** is 285° and that the reported melting point, 235°, is a typographical error.

α-xanthatoalkanones[5,9] free from disulfides is rather difficult, we looked for a simpler method for the regioselective preparation of compound **2**. Alkyl xanthates are known to yield the alkylthiols upon reaction with amines.[10] This cleavage may proceed by direct attack of the amine on the xanthate or on the dithiocarbonate produced by thermal rearrangement of the xanthate.[11] Thus, when cholestan-3-one 2α-xanthate[12] was allowed to react with malononitrile in the presence of morpholine in boiling ethanol, compound **2** was produced. The reaction proceeds through the cholestan-3-one-2α-thiol produced by the direct cleavage of the cholestan-3-one 2α-xanthate since cholestan-3-one-2α-thiol is produced when the xanthate is refluxed in ethanol in the presence of morpholine. The xanthate remains unchanged in boiling ethanol in the absence of the amine or when heated neat at 150°.

During the preparation of the cholestan-3-one-2α-thiol by the known[5] procedure of acid-catalyzed decomposition of the cholestan-3-one 2α-xanthate it was observed that the nature of the solvent employed has a profound effect on the nature of the product formed. While in ether solution the thiol is formed, in benzene solution a new compound is produced in good yield as the only product. The product, $C_{28}H_{44}OS_2$, did not show any absorption above 1700 cm^{-1} in the ir spectrum attributable to a saturated ketone. The nmr spectrum did not have any signal for the vinylic proton. The mass spectrum showed a peak for the molecular ion (*m/e* 460) and a peak (*m/e* 316) due to the loss of fragment ii or iii. On the basis of these data, structure **4** or **5** could be envisaged for the product.

ii iii



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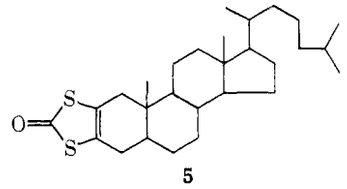
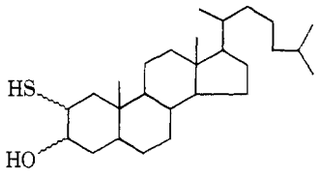


5

The ir spectrum of the compound did not have a strong band[13] for the C=O group of the S–CO–S moiety at 850–827 cm^{-1} and bands above 1650 cm^{-1} attributable to a cyclic dithiocarbonate present in structure **5**.[14] The presence of bands at 1635 and 890 cm^{-1}, on the other hand, suggested[15] that the compound should be represented by structure **4**. This was verified by chemical means. The compound showed positive reaction with iodine–sodium azide solution for the C=S group.[16] Reduction of the product with lithium aluminum hydride gave a small amount of a compound which was identified as the 3-hydroxycholestane-2-thiol (**6**).



6

The ir spectrum showed a band at 3400 cm^{-1} for the OH group. The mass spectrum had peaks at *m/e* 420 (M^+), 402 ($M^+ - H_2O$), and 386 ($M^+ - H_2S$).

Experimental Section[17]

2′-Aminocholest-2-eno[2,3-*b*]thiophene-4′-carbonitrile (2). **A.**—A thoroughly stirred mixture of cholestan-3-one (3.86 g), malonitrile (0.66 g), sulfur (0.32 g), and morpholine (2 ml) in dry ethanol was heated at 48° for 5 hr. The reaction mixture was cooled and the precipatate was filtered and washed with ethanol. The colorless solid, mp 270–278° dec, crystallized from THF–methanol as colorless needles: 2.5 g (54%); mp 279–281° dec (lit.[1,8] mp 235°); ir (KBr) 3480, 3220, 2200, 1645, 1600, 1530 cm^{-1}; uv max ($CHCl_3$) 242 nm (ε 5499), 290 (5326); mass spectrum *m/e* 466 (M^+), 353 ($M^+ - C_8H_{17}$), 150.

Anal. Calcd for $C_{30}H_{46}N_2S$: C, 77.19; H, 9.93; N, 6.0; S, 6.87. Found: C, 77.22; H, 9.93; H, 5.91; S, 6.69.

B.—Cholestan-3-one-2α-thiol (0.5 g) in ether (20 ml) solution was treated with dry ethanol (10 ml), morpholine (5 drops), and malonitrile (0.15 g) and the mixture was heated on the steam bath for 0.5 hr. The solid was filtered and washed successively with ether and ethanol, when a yellowish solid, mp 267–278° dec, was obtained which on recrystallization from THF–methanol gave colorless needles (0.23 g), mp 283–284° dec. This material was identical with the material prepared in A by mixture melting point and ir comparison.

C.—A mixture of cholestan-3-one 2α-ethyl xanthate (0.5 g), ethanol (25 ml), malononitrile (0.2 g), and morpholine (4 drops) was heated on a steam bath for 3 hr. The precipitate was filtered and washed with ethanol. The solid (0.3 g), mp 270–275° dec, was crystallized from THF–methanol and $CHCl_3$–methanol, when pale yellow needles (170 mg), mp 283–285° dec, found identical with the material prepared in B by mixture melting point and ir comparison, were obtained.

2′-Thiocholest-2-eno[2,3-*d*][1,3]oxathiolane (4).—To a solution of cholestan-3-one 2α-ethyl xanthate (3.5 g) in benzene (70 ml) cooled in an ice bath, HCl gas was bubbled in. The solution started to solidify in a few minutes, when the ice bath was removed and HCl was bubbled in for a further 40 min. The flask was tightly stoppered and left at room temperature for 48 hr. The benzene was removed on a steam bath by blowing in nitrogen. The residue was dissolved in benzene and the solution was filtered through silica (25 g) and eluted with benzene (300 ml), when a solid (3.2 g) was obtained which on crystallization from ether (charcoal) gave colorless needles (1.8 g), mp 135–136°. The residue from the mother liquor was chromatographed on silica (60 g) and eluted with benzene–petroleum ether (bp 30–60°) (1:1), when a solid was obtained which on crystallization from ether afforded colorless needles (0.7 g), mp 135–136°, identi-

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(17) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Unless otherwise stated, ir and uv spectra were determined for chloroform and methanol solutions, respectively. Nmr spectra were determined for deuteriochloroform solutions with tetramethylsilane as internal reference and mass spectra were determined on a MS30 instrument at 70 eV. Silica for chromatography refers to Mallinckrodt SilicAR CC-7.

cal with previous crop (mixture melting point, ir, tlc): ir 1635, 1500, 860, 890 cm^{-1}; uv 275 nm (ϵ 2930), 238 (2300); nmr no signal above δ 2.4 ppm; mass spectrum *m/e* 460 (M^+), 445 ($M^+ - CH_3$), 432 ($M^+ - CO$), 400 ($M^+ - COS$), 316 ($M^+ - 144$).

Anal. Calcd for $C_{28}H_{44}OS_2$: C, 72.98; H, 9.63; S, 13.92. Found: C, 72.61; H, 9.48; S, 13.64.

Lithium Aluminum Hydride Reduction of 3.—A solution of **3** (0.5 g) in ether (50 ml) was added to a suspension of lithium aluminum hydride (2 g) in ether (100 ml); the mixture was refluxed for 32 hr, cooled, and decomposed with a saturated solution of Na_2SO_4 and then treated with dilute hydrochloric acid (10%) till acidic. The ether layer was separated and the aqueous portion was extracted with ether (140 ml). The combined ether solution was washed with water, dried (Na_2SO_4), and evaporated, when a colored oil (0.31 g) was obtained which was found to be a complex mixture of products by tlc. This was chromatographed on silica (25 g). Elution with benzene–petroleum ether (2:1) gave a highly colored oil (a complex mixture by tlc) (0.15 g) which could not be purified and identified. Elution of the column with benzene gave a solid (60 mg), which on several crystallizations from ether–methanol gave a colorless solid: mp 173–177° (sintering at 171°); ir 3400, 800 cm^{-1}; nmr δ 3.3–4.1 ppm (broad, 2 H); mass spectrum *m/e* 420 (M^+), 405 ($M^+ - CH_3$), 402 ($M^+ - H_2O$), 387 ($M^+ - SH$), 386 ($M^+ - H_2S$).

Anal. Calcd for $C_{27}H_{48}OS$: C, 77.06; H, 11.60. Found: C, 77.20; H, 11.48.

Cholestan-3-one-2α-thiol.—A solution of cholestan-3-one 2α-ethyl xanthate (0.5 g) in dry ethanol (30 ml) containing morpholine (5 drops) was refluxed in a nitrogen atmosphere for 5 hr. The solvent was removed and the residue was chromatographed on silica (25 g) using benzene–petroleum ether (1:1) as eluent, when a solid (0.22 g) was obtained which upon crystallization from ether–methanol in a nitrogen atmosphere gave colorless needles (0.172 g), mp 154–158°. This was found to be the cholestan-3-one-2α-thiol by comparison of ir, nmr, and uv spectra with those of an authentic sample prepared by the known[5] procedure. However, when the reaction was carried out in the presence of air, the only identifiable product was the bischolestan-3-one 2,2′-disulfide[5] (identity established by mixture melting point, ir, and tlc comparison with an authentic sample).

Attempted Rearrangement of Cholestan-3-one 2α-Ethyl Xanthate. A.—The xanthate (50 mg) was heated at 150° for 0.5 hr The residue was found to be identical with starting material by tlc (single spot with R_f identical with that of the starting material) and ir comparison.

B.—A solution of the xanthate (0.2 g) in dry ethanol (25 ml) was refluxed for 6 hr. The solution was filtered from a small amount of insoluble residue and then concentrated. The oily residue was chromatographed on silica. Elution of the column with benzene–petroleum ether (1:2) gave an oil which on crystallization from methanol gave a solid (115 mg), mp 115–116°, identical with the starting material by mixture melting point and ir comparison.

Acknowledgment.—The author wishes to thank Dr. J. W. Ahlberg and his associates for analytical and spectral data and Dr. J. Hribar for mass spectral data and assistance in the interpretations.

Registry No.—**2**, 42086-95-3; **4**, 42086-96-4; cholestan-3-one, 15600-08-5; cholestan-3-one-2α-thiol, 42086-97-5; cholestan-3-one 2α-ethyl xanthate, 42086-98-6; malononitrile, 109-77-3.

Cyclopropylamine Rearrangement[1]

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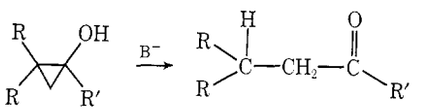
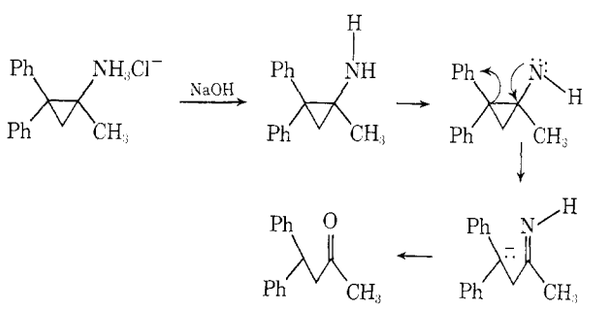
The cyclopropanol rearrangement was originally observed by Magrane and Cottle[2] and extensively explored by DePuy and coworkers.[3] The rearrangement involves the reaction of cyclopropanols with base to yield the corresponding aldehydes or ketones.



In a recent paper Kuehne and King[4] noted that cyclopropylamines were remarkably stable toward both acidic and basic conditions. The amines studied were all tertiary amines and therefore lacking amino hydrogens. We wish to report an example in which a facile rearrangement, comparable with the cyclopropanol rearrangement, occurs when a primary cyclopropylamine reacts with base. A similar rearrangement has been postulated for the hydride reduction of *N*-cyclopropylimines[5] and *N*-cyclopropylformamide[6] derivatives. However, it is not clear from these latter experiments whether the rearrangement occurs during hydride reduction as postulated by these workers or during the subsequent base work-up of the reduction product.

1-Methyl-2,2-diphenylcyclopropylamine was prepared by refluxing 1-methyl-2,2-diphenylcyclopropyl isocyanate[7] with hydrochloric acid. The amine is isolated as its stable hydrochloride salt. Treatment of the amine salt with aqueous or methanolic sodium hydroxide results not in the formation of the free cyclopropylamine but rather one obtains 4,4-diphenyl-2-butanone as the sole product. The propensity for this rearrangement is remarkable since one can achieve this reaction by treatment of the amine salt with aqueous sodium bicarbonate.



The scope, limitations, and stereochemistry of the cyclopropylamine rearrangement are currently under investigation.

Experimental Section

1-Methyl-2,2-diphenylcyclopropylamine Hydrochloride.—A solution of 7.2 g (0.29 mol) of 1-methyl-2,2-diphenylcyclopropyl isocyanate,[7] 45 ml of concentrated hydrochloric acid, and 90 ml of water was refluxed overnight. On cooling the amine hydrochloride precipitated out of solution and was removed by filtration,

(1) The support of this work by a Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.

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