TABLE I

DI-(4-NITROPHTHALIMIDO)-ALKANES AND BIS-(4-NITROPHTHALIMIDOALKYL) ETHERS

Dihalide	Heating time, hr.	Yield, %[a]	M.p., °C.[b]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Dibromomethane	1.5	2.5	223–224	$C_{17}H_8N_4O_8$	14.14	14.21
	4.0	28.7	223–224			
1,2-Dibromoethane	3.0	44.6	289–290	$C_{18}H_{10}N_4O_8$	13.66	13.63
1,3-Dibromopropane	1.5	18.8	202.5–203.5	$C_{19}H_{12}N_4O_8$	13.20	13.16
1,4-Dibromobutane	1.5	65.0	263–264	$C_{20}H_{14}N_4O_8$	12.78	12.85
1,5-Dibromopentane	2.0	49.2	195–196	$C_{21}H_{16}N_4O_8$	12.39	12.36
1,6-Dibromohexane	1.5	55.4	213–214	$C_{22}H_{18}N_4O_8$	12.01	11.99
1,7-Dibromoheptane	1.5	16.5	169–170	$C_{23}H_{20}N_4O_8$	11.66	11.56
	3.0	62.1	169–170			
1,9-Dibromononane	1.5	29.9	146–147	$C_{25}H_{24}N_4O_8$	11.02	11.00
1,10-Dibromodecane	2.0	53.0	175–176	$C_{26}H_{26}N_4O_8$	10.72	10.82
Bis-(β-chloroethyl) ether	3.0	21.7	198.5–199.5	$C_{20}H_{14}N_4O_9$	12.33	12.43
Bis-(β-chloroisopropyl) ether	3.0	27.6	131–132	$C_{22}H_{18}N_4O_9$	11.61	11.52

[a] Yield after recrystallization, based on dihalide. [b] Melting points over 260° are uncorrected and taken on a Fisher-Johns apparatus.

ethyl alcohol nearly to the point of cloudiness. If the product would not largely dissolve in chloroform, dimethylformamide was used in a like manner. The purified products were cream-colored solids.

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Preparation of Ethylenethioketals

BY LOUIS F. FIESER

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Previous methods for effecting the condensation of ketones with ethanedithiol or β-mercaptoethanol include use of zinc chloride and sodium sulfate,[1,2] hydrogen chloride in ether,[3,4] *p*-toluenesulfonic acid in benzene with azeotropic distillation[5,6] and an exchange method.[6] Two much simpler procedures that appear to be of comparable applicability utilize boron fluoride etherate as the condensing agent. In several instances addition of boron fluoride etherate to an acetic acid solution of ketone and excess mercaptan at room temperature results in prompt separation of the thioketal or hemithioketal derivative in high yield. An alternative procedure is to add boron fluoride etherate to a suspension or solution of the ketone in ethanedithiol; this reagent has remarkable power for dissolving steroid ketones. That the second procedure is more vigorous than the first is evidenced by the observation that B-norcoprostane-3,6-dione gave only oils when treated with ethanedithiol and boron fluoride etherate in acetic acid or methanol but afforded the bis-ethylenethioketal in high yield in the absence of solvent.[7] Neither procedure seems to be applicable to the condensation of ethylene glycol with such ketones as the 3-one, 3,6-dione and Δ^4-3,6-dione derivatives of cholestane.[8]

The possibility of investigating the structure of an unknown diketone by converting it into a monoethylenethioketal that could be degraded to recognizable products by desulfurization, or by Wolff-Kishner reduction followed by desulfurization, was tested with the model compounds cholestane-3,6-dione and Δ^4-cholestene-3,6-dione. Both diketones gave bis-ethylenethioketal derivatives in high yield with excess reagent, but on condensation with one equivalent of ethanedithiol in acetic acid in the presence of boron fluoride etherate each substance afforded a monoethylenethioketal, isolated by crystallization or by chromatography. Desulfurization of both mono derivatives with Raney nickel gave cholestane-6-one, and hence in each instance selective condensation with ethanedithiol occurs at the 3-keto group; desulfurization of Δ^4-cholestene-3,6-dione 3-monoethylenethioketal is attended with saturation of the double bond unless the Raney nickel is deactivated by refluxing it with acetone.[9] On reaction with excess ethanedithiol in acetic acid solution, benzil was found to yield only a monoethylenethioketal ketone. Whereas the 6β- and 6α-hydroxy derivatives of Δ^4-cholestene-3-one reacted with ethanedithiol to give cholestane-3,6-dione bis-ethylenethioketal (m.p. 220°) (as did Δ^5-cholestene-4α-ol-3-one acetate[10]), Δ^4-cholestene-6β-ol-3-one acetate gave an isomeric substance, m.p. 132°. An additional isomeric bis-ethylenethioketal (m.p. 280°) has been obtained from the condensation of ethanedithiol with Δ^4-cholestene-3β-ol-6-one acetate, and an investigation of the structure of these two isomers is in progress.

For exploration of possible molecular rotation relationships some additional cyclic ketal derivatives of monoketones were prepared and characterized, with the results summarized in Table I. Of the three derivatives of dehydroepiandrosterone acetate, the hemithioketal differs in *M*D more from the parent ketone than either of the symmetrical derivatives, and in the cholestanone series the hemithioketal shows a greater increment than the dithio

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[1] H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

[2] J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 4961 (1951).

[3] J. W. Rolls, R. M. Dodson and B. Riegel, *ibid.*, **71**, 3320 (1949).

[4] F. Kipnis and J. Ornfelt, *ibid.*, **71**, 3555 (1949).

[5] E. P. Oliveto, T. Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953).

[6] C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

[7] L. F. Fieser, *ibid.*, **75**, 4386 (1953).

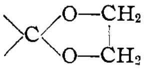
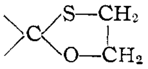
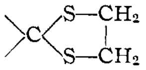
[8] However, H. Koster and H. H. Inhoffen, U. S. Patent 2,302,636 (1942), found that stannic chloride in carbon tetrachloride effectively catalyzes the reaction of ketones with ethylene oxide.

[9] G. B. Spero, A. V. McIntosh, Jr., and R. H. Levin, THIS JOURNAL, **70**, 1907 (1948); G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

[10] L. F. Fieser and R. Stevenson, manuscript submitted for publication.

TABLE I

MOLECULAR ROTATIONS (INCREMENTS IN PARENTHESES)

Ketone	$>C=O$			
Dehydroepiandrosterone acetate	−23	−313 (−290)	−389 (−366)	−351 (−328)
Cholestanone	+158		+111 (−47)	+148 (−10)
Δ^5-Cholestene-3-one	−18	−135	−87 (−69)	
Δ^4-Cholestene-3-one	+342			+549 (+207)
Cholestane-3,6-dione 3-monoethylenethioketal	+7			+116 (+109)
Δ^4-Cholestene-3,6-dione 3-monoethylenethioketal	−160			+386 (+546)

derivative. The increments are far greater with the 17-keto than with the 3-keto derivatives (compare Djerassi[6]) because C_{17} is adjacent to a center of asymmetry while C_3 is not, but the increments are in all these cases negative, as is that for the hemithioketal of Δ^5-cholestene-3-one. The relationship appears different for conjugated and non-conjugated ketones. That the MD increment for conversion of cholestane-3,6-dione into the 3-monoethylenethioketal is strongly positive indicates that comparison with the case of cholestanone is vitiated by a vicinal effect associated with the presence of a 6-keto group adjacent to the asymmetric center at C_5.

Experimental

Cholestane-3,6-dione Bis-ethylenethioketal.—A mixture of 180 mg. of cholestane-3,6-dione and 0.2 cc. of ethanedithiol (Aldrich Chemical Co.) in a test-tube was treated with 0.2 cc. of boron fluoride etherate and the mixture homogenized with a stirring rod. The mixture became warm and soon set to a stiff paste of white solid. After 5 min., 8 cc. of methanol was added, the mixture was stirred well and cooled, and the solid collected and washed with methanol; yield 233 mg. (94%), m.p. 217–219°. Crystallization from hexane gave well-formed needles, m.p. 219–220°, αD +30.4° Chf (*c* 1.09).

Anal. Calcd. for $C_{31}H_{52}S_4$ (552.73): C, 67.36; H, 9.48. Found: C, 67.40; H, 9.53.

An identical product was obtained by the same procedure in lower yield from Δ^4-cholestene-6β-ol-3-one (278 mg. gave 112 mg. of pure product, m.p. and mixed m.p. 218–219°) and from Δ^4-cholestene-6α-ol-3-one (146 mg. gave 52 mg., m.p. and mixed m.p. 218–219°).

Reduction was accomplished by refluxing 150 mg. of the bis-ketal with excess Raney nickel in absolute ethanol overnight and collecting the product by ether extraction of the filtered solution. Crystallization from methanol–ether gave 40 mg. of plates of **cholestane**, m.p. 77–78°, undepressed on admixture with an authentic sample.

Isomeric Bis-ethylenethioketal.—One gram of Δ^4-cholestene-6β-ol-3-one acetate was dissolved in 1 cc. of ethanedithiol by gentle warming and the solution was cooled to room temperature and treated with 1 cc. of boron fluoride etherate. A stiff orange paste soon resulted, and after 5 min. this was thinned with 5 cc. of acetic acid and the white solid was collected and washed with methanol; yielded 0.97 g., m.p. 127–129°. Attempted crystallization from a variety of solvents failed to give satisfactory crystals. When chromatographed the material appeared to be homogeneous and was eluted readily from alumina by 4:1 petroleum ether–benzene. The resulting glass was dissolved in hot acetic acid and the solution on cooling deposited a white non-crystalline powder. Two more attempted crystallizations from ethyl acetate (very soluble)–methanol (sparingly soluble) gave an amorphous powder, m.p. 130–132°; the infrared spectrum was undistinguished but definitely devoid on bands associated with carbonyl or acetate functions. A substance of similarly ill-defined properties and spectrum was obtained from Δ^4-cholestene-6α-ol-3-one acetate.

Anal. Calcd. for $C_{31}H_{52}S_4$ (552.73): C, 67.36; H, 9.48; S, 23.20. Found: C, 67.71; H, 9.58; S, 22.86.

Cholestane-3,6-dione 3-Monoethylenethioketal.—A solution of 2 g. of cholestane-3,6-dione in 80 cc. of acetic acid was treated at 25° with 45 cc. of acetic acid containing 0.6 g. of ethanedithiol and 8 cc. of boron fluoride etherate. After 5 hr., a precipitate of 0.85 g. of bis-ketal, m.p. 215–127°, was collected and the material recovered from the filtrate by ether extraction was chromatographed. Petroleum ether–benzene (3:1) eluted a series of fractions of solid product that on crystallization from methanol afforded 0.67 g. of satisfactory monoketal, m.p. 130–131°. Recrystallized from methanol, in which it is sparingly soluble, the substance formed flat needles, m.p. 131–132°, αD + 24.4° Chf (*c* 2.09), λ^{Chf} 5.87 μ.

Anal. Calcd. for $C_{29}H_{48}OS_2$ (476.67): C, 73.07; H, 10.15. Found: C, 73.27; H, 10.18.

Desulfurization[11] was accomplished by refluxing 0.62 g. of the monothioketal derivative (m.p. 128–130°) with Raney nickel in dioxane for 7 hr. The solution was filtered through Supercel and the nickel washed thoroughly with warm dioxane and then with ether. Evaporation of the solvents left a residue of 0.38 g. of solid, m.p. 81–88°. Crystallization from acetone–methanol gave 0.3 g. of white leaflets, m.p. 94.5–96°, and after five further crystallizations the sample of **cholestane-6-one** had the constants: m.p. 101–102°, αD +2.2° Chf (*c* 1.95), λ^{Chf} 5.87 μ; oxime, m.p. 189–193° dec. (lit., ketone,[12] m.p. 99–100°), λ^{Chf} 5.79 μ; oxime,[13] m.p. 189–193° dec. The substance did not depress the m.p. of a sample of cholestane-6-one (m.p. 99–101°) kindly supplied by Dr. C. W. Shoppee.

Δ^4-Cholestene-3,6-dione Bis-ethylenethioketal.—A solution of 1 g. of Δ^4-cholestene-3,6-dione, m.p. 124–125°, in 20 cc. of acetic acid was cooled to 25° and treated with 0.5 cc. of ethanedithiol and 1 cc. of boron fluoride etherate. A stiff paste of product soon resulted; a little methanol was added for thinning and the white solid collected and washed with methanol: 1.1 g., m.p. 181–184°. Crystallization from dioxane–ethanol gave poor results, but the substance crystallized nicely from acetic acid (moderately soluble hot) to give 0.8 g. of pure product, m.p. 202–203°, αD +86.1° Chf (*c* 1.21); unsaturated to tetranitromethane.

Anal. Calcd. for $C_{31}H_{50}S_4$ (550.71): C, 67.61; H, 9.15. Found: C, 67.45; H, 9.03.

Reduction of this derivative by refluxing with Raney nickel and absolute ethanol overnight gave a substance that on crystallization from methanol containing a little ether formed thin plates, m.p. 65–66°; recrystallized, m.p. 66–67°, αD +15° Chf (*c* 1.79).

Anal. Calcd. for $C_{27}H_{46}$ (370.64): C, 87.49; H, 12.51. Found: C, 87.23; H, 12.76.

The material is probably a mixture of Δ^4-cholestene, m.p. 82–83.5°; αD +76° Chf,[14] and Δ^5-cholestene, m.p. 92.5–94°, αD −56° Chf.[14]

Δ^4-Cholestene-3,6-dione 3-Monoethylenethioketal.—A solution of 1 g. of the enedione in 40 cc. of acetic acid was treated at 25° with 22 cc. of a solution of 1.33 g. of ethane-

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[11] Experiment by Ching Yuan.

[12] H. Reich, *J. Org. Chem.*, **16**, 1760 (1951).

[13] A. Windaus, *Ber.*, **53**, 495 (1920).

[14] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *J. Chem. Soc.*, 2402 (1951).

dithiol in 100 cc. of acetic acid, followed by 4 cc. of boron fluoride etherate. Crystals of the high-melting bis-product started separating in about one-half hour; after standing overnight the crystallized bis-product was collected (0.55 g.) and the material in the mother liquor recovered by ether extraction. A little starting material was removed by extraction of a petroleum ether solution of the product with Claisen's alkali. After concentration of the petroleum ether solution, the monoketal separated in crystalline condition, m.p. 156° (0.3 g.). The substance is sparingly soluble in methanol and readily soluble in hot hexane. It crystallized slowly from hexane in massive clusters of short needles, m.p. 158.5–159.5°, α_{D} +81.2° Chf (*c* 2.03), λ^{EtOH} 244 mμ (7,170), λ^{Chf} 5.93, 6.19 μ.

Anal. Calcd. for $C_{29}H_{46}OS_2$ (474.66): C, 73.38; H, 9.77. Found: C, 73.48; H, 9.73.

Desulfurization of this product with active Raney nickel was accomplished by refluxing in dioxane for 7 hr.[15] or in absolute ethanol for 9 hr.[11] In the first case, 1.5 g. of derivative gave 0.65 g. of white solid m.p. 88–93°, and five recrystallizations gave glistening white leaflets of **cholestane-6-one**, m.p. 97–99°, α_{D} +2.5° Chf (*c* 1.83), λ^{Chf} 5.87 μ, no ultraviolet absorption at 243 mμ; oxime, m.p. 186–191° dec., no depression on admixture with the above sample. Desulfurization[11] in boiling dioxane (7 hr.) with Raney nickel deactivated by refluxing it with acetone[9] and chromatography of the product gave Δ^4-cholestene-6-one as needles from ethanol, m.p. 108–109°, α_{D} +31.6° Chf (*c* 1.43), λ^{Chf} 6.00, 6.20 mμ, λ^{EtOH} 242 mμ (3,846); this did not depress the m.p. of an authentic sample of comparable constants.

Cholestane-3-one Ethylenethioketal.—A solution of 600 mg. of cholestanone and 1 cc. of ethanedithiol in 15 cc. of hot acetic acid was treated with 1 cc. of boron fluoride etherate and let stand to crystallize. Excellent needles separated and were collected and washed with methanol; 662 mg. (92%), m.p. 142–144°. Recrystallization from acetone or from dioxane–ethanol gave long flat needles, m.p. 146.5–147.5°, α_{D} +32.0° Chf (*c* 2.09).

Anal. Calcd. for $C_{29}H_{50}S_2$ (462.69): C, 75.28; H, 10.89. Found: C, 75.11; H, 10.88.

Cholestane-3-one Ethylenehemithioketal (*cf.* ref. 6).—A solution of 130 mg. of cholestanone in 6 cc. of acetic acid was treated at 25° with 0.2 cc. of β-mercaptoethanol and 0.5 cc. of boron fluoride etherate and left undisturbed. Crystallization soon commenced, and when it seemed complete, methanol was added and the product collected; 124 mg., m.p. about 130°. The substance is only moderately soluble in ethanol and separated in glistening slender needles, m.p. 133–134° (104 mg.); recrystallized, m.p. 133–134°, α_{D} +24.8° Chf (*c* 0.681).

Anal. Calcd. for $C_{29}H_{50}OS$ (446.69): C, 77.97; H, 11.28. Found: C, 78.34; H, 11.40.

Δ^5-Cholestene-3-one Ethylenehemithioketal.—On addition of 0.4 cc. of β-mercaptoethanol and 1 cc. of boron fluoride etherate to a suspension of 368 mg. of Δ^5-cholestene-3-one in 10 cc. of acetic acid at 25°, the reaction product started to separate before the ketone had all dissolved. The mixture was stirred well, diluted with methanol, and 100 mg. of product collected (m.p. about 130°). This crystallized nicely from ethanol in cottony clusters of fine needles (76 mg.), m.p. 136–137° (unchanged on recrystallization, α_{D} −19.6° Chf (*c* 0.847).

Anal. Calcd. for $C_{29}H_{48}OS$ (444.67): C, 78.32; H, 10.88. Found: C, 78.57; H, 11.11.

The low yield is undoubtedly because of isomerization to the conjugated ketone before condensation is complete. Thus attempted condensation of 307 mg. of Δ^5-cholestene-3-one with ethylene glycol under comparable conditions afforded 114 mg. of Δ^4-cholestene-3-one, m.p. 80–81°, mixed m.p. 81–82°.

Derivatives of Dehydroepiandrosterone. (a) **Ethylenethioketal Acetate.**—A solution of 300 mg. of dehydroepiandrosterone acetate, 0.3 cc. of ethanedithiol and 0.3 cc. of boron fluoride etherate in acetic acid at 25° soon deposited crystals. A little water was added and the crystals were collected and washed with methanol; 343 mg. m.p. 190°. The derivative crystallized from 95% ethanol in large, thin plates, m.p. 191–192°, α_{D} −86.4° Chf (*c* 2.14).

Anal. Calcd. for $C_{23}H_{34}O_2S_2$ (406.50): C, 67.95; H, 8.43. Found: C, 68.03; H, 8.46.

(b) **Ethylenehemithioketal Acetate.**—Similar condensation of 300 mg. of the acetate with β-mercaptoethanol gave 310 mg. of product, m.p. 166–170°. Crystallized from 95% ethanol, the substance formed long blades, m.p. 183–184° (unchanged on recrystallization), α_{D} −99.5° Chf (*c* 2.08).

Anal. Calcd. for $C_{23}H_{34}O_3S$ (390.50): C, 70.74; H, 8.78. Found: C, 70.72; H, 8.82.

(c) **Ethyleneketal.**[16]—A solution of 1.5 g. of dehydroepiandrosterone and 1.5 g. of ethylene glycol in 80 cc. of benzene was distilled in a water separator until dry, 100 mg. of *p*-toluenesulfonic acid was added, and the solution was refluxed overnight in the water take-off apparatus. Ether extraction and crystallization from aqueous methanol (with addition of a drop of pyridine) gave 1.0 g. (59%) of product, m.p. 161–165°.

Anal. Calcd. for $C_{21}H_{32}O_3$ (332.47): C, 75.86; H, 9.71. Found: C, 75.71; H, 9.80.

The acetate crystallized from aqueous methanol in beautiful plates, m.p. 140–142°, α_{D} −83.5° Chf (*c* 2.06).

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.53; H, 9.31.

(d) **3β-Acetoxy-Δ^5-androstene-7-one 17-Ethyleneketal**[16] was obtained by chromic acid oxidation of the acetate (c) at 55–60° (5 hr.). The keto derivative, crystallized from aqueous methanol, melted at 175–177°, $\lambda^{\mathrm{CCl_4}}$ 5.95 μ.

Anal. Calcd. for $C_{23}H_{32}O_3$ (388.49): C, 70.95; H, 8.51. Found: C, 71.10; H, 8.30.

Δ^4-Cholestene-3-one Ethylenethioketal.—A solution of 1 g. of Δ^4-cholestene-3-one in 5 cc. of acetic acid, treated at 25° with 0.5 cc. of ethanedithiol and 0.5 cc. of boron fluoride etherate, warmed up and in 1–2 min. set to a stiff paste. After 15 min. the product was collected and washed with methanol: 1.15 g. (96%), m.p. 117–118°. Crystallization from acetone–methanol gave slender, flat needles, m.p. 117.5–118.5°; recrystallized: 118.5–119.5°, α_{D} + 111.8° Chf (*c* 2.03); Hauptmann,[1] m.p. 106–107°, α_{D} + 119° Chf.

Anal. Calcd. for $C_{29}H_{48}S_2$ (460.67): C, 75.60: H, 10.50. Found: C, 75.38; H, 10.58.

Benzil Monoethylenethioketal.—A solution of 1 g. of benzil in 4 cc. of acetic acid at 25° was treated with 1 cc. each of ethanedithiol and boron fluoride etherate and let stand undisturbed. The yellow color was slowly discharged after about one day, and on the second day the product separated in large prismatic needles; 1.0 g., m.p. 93–94°. Recrystallization from ethanol (best by seeding) raised the m.p. to 95–96°, λ^{Chf} 5.97, 6.25, 6.31 μ.

Anal. Calcd. for $C_{16}H_{14}OS_2$ (286.27): C, 67.12; H, 4.93. Found: C, 66.85; H, 4.87.

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(15) Experiment by Freeland E. Romans.

(16) Experiment by Josef E. Herz.

CAMBRIDGE, MASS.

9-Methyl-3,9-diazatricyclo[3.3.1.2^{3,9}]undecane

BY HENRY M. FALES AND RODERICK A. BARNES

RECEIVED DECEMBER 28, 1953

In a recent description of the synthesis of the 3,9-diazabicyclo[3.3.1]nonane ring system[1] the possibility of linking the two nitrogen atoms with an ethylene bridge was mentioned. With the realization of this possibility we have now prepared the first example of a substance in which four six-membered rings are linked in this kind of tricyclic system.

Ethylene bromide reacted smoothly with 9-methyl-3,9-diazabicyclo[3.3.1]nonane (I) in toluene at 40°. Both the crystalline bromide and picrate salts of the resulting quaternary ammonium base II were obtained.

The only substances, other than II, which could logically have the observed analysis are the 3- or 9-vinyl derivatives of I or a dimeric product re-

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(1) R. A. Barnes and H. M. Fales, THIS JOURNAL, **75**, 975 (1953).