washed once with chloroform (30 ml). The chloroform was evaporated on the rotary evaporator yielding 0.0965 g (90%) of **7** as a crude product. The nmr and infrared spectra showed no trace of starting material in the crude product. Recrystallization from benzene–pentane (1:1) gave **7** as yellow plates: mp 49.9–50.4°; $\lambda_{max}^{95\%\ EtOH}$ 245 mμ (ε 13,700).[8] The infrared spectrum of **7** ($CHCl_3$) showed broad carbonyl absorption at 5.85–5.95 μ. The nmr spectrum (CCl_4) of **7** showed peaks at 6.49 (1 H, multiplet, olefinic), 2.41 (3 H, singlet, methyl), and 2.63–1.83 ppm (6 H, multiplet).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.00; H, 7.26.

Preparation of 3-Acetyl-2-cyclohexenone (7) from 2-Methyl-2-(1-cyclohexen-3-one)-1,3-dithiane (5).—A solution of acetonitrile (10 ml), water (4 ml), silver nitrate (0.348 g, 2.05 mmoles), and N-chlorosuccinimide (0.243 g, 1.82 mmoles) was cooled to 0°. A solution of **5** (0.104 g, 0.46 mmole) dissolved in acetonitrile (5 ml) was added dropwise to the stirred reaction mixture followed by a 1-ml acetonitrile rinse. The reaction was carried out under a nitrogen atmosphere and kept at 0° for 25 min. Dimethyl sulfoxide (1 ml) was added after 25 min and the reaction mixture was subsequently warmed to room temperature for 30 min. The reaction mixture was filtered and the filtrate was extracted with chloroform. The organic layer was washed with an aqueous ammonium acetate solution. The aqueous phase was extracted three times with chloroform and the combined chloroform extracts were washed once with water, once with a saturated sodium chloride solution, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the residue was put through a 1 × 1.5 cm silica gel column. The column was eluted with 30 ml of benzene which after evaporation yielded **7** (0.0625 g, 100%) as yellow crystals, which were shown to be pure by nmr and tlc analysis. Sublimation at a bath temperature of 45° (0.01 mm) gave pure **7** whose melting point (49.8–50.3°) and infrared and nmr spectra were identical with those of a sample prepared by oxidizing 3-acetyl-2-cyclohexenol.

Preparation of 3-Acetylcyclohexanone (8) from 3-Acetyl-2-cyclohexenol (6).—A solution of **6** (0.463 g, 3.81 mmoles) and potassium hydroxide (0.224 g, 4.0 mmoles) in methanol (30 ml) and water (3 ml) was refluxed in a nitrogen atmosphere. After 14 hr, 50 ml of water was added to the reaction mixture and this solution was extracted three times with chloroform (50 ml each). The combined chloroform extracts were washed once with an aqueous sodium bicarbonate solution, twice with water, once with an aqueous sodium chloride solution, and dried (Na_2SO_4). The solvent was removed with a rotary evaporator yielding **8** (0.450 g, 97% yield) as a clear crude oil, bp 79–81° (0.02 mm) (lit.[9] bp 140–145°, (15 mm)). Nmr and tlc analysis of the crude product showed the absence of **6**. After distillation the oil crystallized on standing, mp 37.4–38.3° (lit.[9] mp 39°). The molecular weight determined mass spectrometrically was 140.0837 (calcd for $C_8H_{12}O_2$, 140.0837). The infrared spectrum (neat) of **9** showed a broad carbonyl absorption at 5.8–5.9 μ. The nmr spectrum (CCl_4) exhibited peaks at 3.03–2.53 (1 H, multiplet), 2.14 (3 H, singlet, methyl), and 2.42–1.45 ppm (8 H, multiplet).

Preparation of 3-Acetylcyclohexanone (8) from 3-Acetyl-2-cyclohexenone (7).—Compound **7** (0.099 g, 0.718 mmole) was dissolved in acetic acid (10 ml) and water (3 ml) and stirred at room temperature in the presence of powdered zinc (0.510 g, 7.81 mmoles). After 4.5 hr the reaction mixture was filtered, diluted with water (50 ml), and extracted four times with chloroform. The combined chloroform extracts were washed twice with an aqueous sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed with a rotary evaporator yielding **8** (0.098 g, 98% yield) as a crude product. The melting point (37.2–38.3°) and infrared and nmr spectra were identical with those of **8** obtained under basic conditions from 3-acetyl-2-cyclohexenol. The crude product contained no **7** or solvent by nmr and tlc analysis.

Registry No.—**3**, 15040-92-3; **4**, 15040-93-4; **5**, 15040-94-5; **6**, 15040-95-6; **7**, 15040-96-7; **8**, 15040-97-8.

Acknowledgment.—This work was supported in part by the National Institutes of Health. We are grateful to Drs. Dieter Seebach and Tony Durst for helpful discussions.

(8) C. Amendolla, G. Rosenkranz, and F. Sondheimer,[7] have reported, for cholest-4-ene-3:6-dione, λ_{max} 250 mμ (ε 11,200).

(9) A. McCoubrey, *J. Chem. Soc.*, 2931 (1951).

A New Synthetic Route to Cyclic Mono- and Diketone Derivatives *via* Bisthio Carbanions

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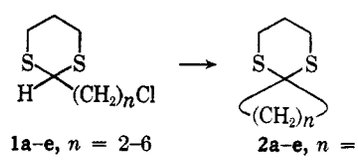
Received August 24, 1967

The synthesis of a series of 1,3-propylene thioketal derivatives of cyclic ketones having three, four, five, six, and seven ring members is described to illustrate a new method for ring formation which depends on an intramolecular displacement reaction of 2-haloalkyl-1,3-dithianes.

The 2-lithio derivatives of 1,3-dithianes react readily with halides to afford 2-alkylated dithianes in excellent yield.[2a] This paper reports the successful development of the intramolecular analog of this process which provides a new and useful route to a wide range of cyclic mono- and diketones.[2b,c]

In its simplest form the cyclization is illustrated by the conversion of the 2-(ω-chloroalkyl)-1,3-dithianes **1a–e** into the cycloalkanone trimethylenethioketals **2a–e** (see eq 1). The ring closure has been effected



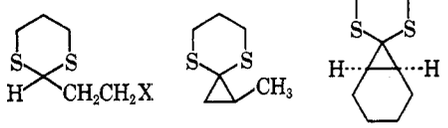
1a–e, n = 2–6 **2a–e**, n = 2–6 (1)

simply by treatment of the chloroalkyldithianes **1** in tetrahydrofuran under nitrogen at −70° to 0° with an equivalent of *n*-butyllithium reagent in hexane. Ring formation proceeded efficiently at normal preparative concentration with uniformly good yields (*ca.* 80%) being obtained in the case of the three, four, five, and six-membered rings. The yield of cyclization product **2e** having a seven-membered ring was somewhat less, 67%. Preliminary studies indicate that the efficiency of cyclization to form an eight-membered ring is very

(1) Undergraduate research student, 1966.

(2) (a) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1075, 1077 (1965). (b) For a preliminary presentation of part of this work, see E. J. Corey, *Pure and Appl. Chem.*, **14**, 19 (1967). (c) Application of 2-lithio-1,3-dithianes to other synthetic problems has been described: E. J. Corey, D. Seebach, and R. Freedman, *J. Am. Chem. Soc.*, **89**, 434 (1967); E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).

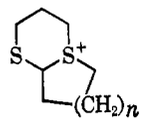
poor at concentrations in the range 0.03–0.08 *M* which were used to produce the smaller rings. The 2-(ω-chloroalkyl)-1,3-dithianes **1b–e** were prepared readily by the alkylation of 2-lithio-1,3-dithiane in tetrahydrofuran *either* with 1 equiv of an ω-chloroalkyl iodide (in which case selective displacement of iodide occurs) or with 2–3 equiv of the appropriate α,ω-dichloroalkane. The former procedure affords higher yields of chloroalkyldithiane **1**, but the latter procedure possesses an advantage in convenience, since the dichlorides are more directly available than chloro iodides. The intermediate **1a** can be prepared either from β-chloroacetaldehyde diethyl acetal and 1,3-propanedithiol or from 2-lithio-1,3-dithiane by hydroxyethylation to **3**, X = OH, with ethylene oxide followed by reaction with thionyl chloride; alternatively, the conversion of **3**, X = OH, to **3**, X = Cl, could be accomplished *via* the intermediate **3**, X = toluenesulfonate, by displacement with chloride ion. The cyclopropanone dithioketal **2a** could be obtained not only from the chloride **1a** but also from the corresponding *p*-toluenesulfonate **3**, X = *p*-Ts. Using a similar sequence *via* *p*-toluenesulfonate



3 **4** **5**

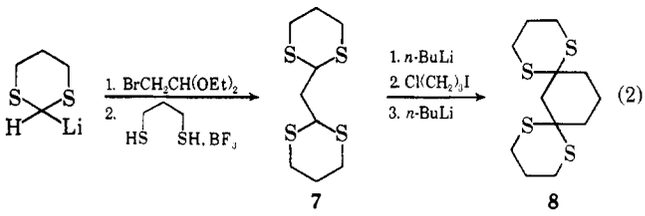
derivatives in the cyclization step propylene oxide and cyclohexene oxide were efficiently converted to **4** and **5**, respectively. In connection with the use of this method for the synthesis of cyclopropanone derivatives, it should be mentioned that 2-haloethyl-1,3-dithianes cannot be prepared satisfactorily by alkylation with 1,2-dihalides, since complex mixtures are produced under the usual reaction conditions.

The use of ω-bromo analogs of the ω-chloroalkyldithianes **1** in the cyclization is impractical because of the ease with which these compounds are transformed into sulfonium bromides. Thus, the sulfonium derivatives **6a** and **6b** were obtained instead of the corresponding ω-bromoalkyldithianes during attempted isolation of the latter.



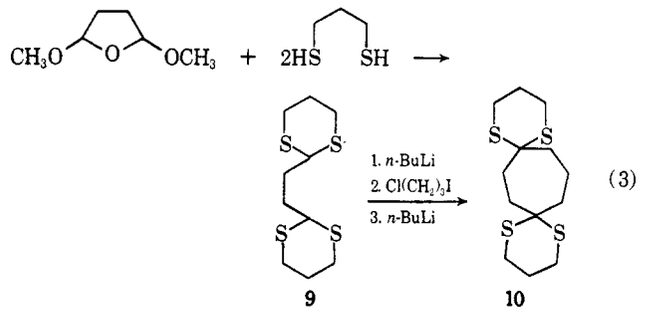
6a, *n* = 1
b, *n* = 2

The conversion of 1,3-dithiane to the spiro derivatives **2** can also be accomplished without isolation of the intermediate ω-chloro compounds **1**. For example, successive treatment of 1,3-dithiane in tetrahydrofuran with equivalent amounts of *n*-butyllithium, 1-iodo-3-chloropropane, and *n*-butyllithium in a single vessel afforded in 50% yield the bisthioketal of cyclohexane-1,3-dione (**8**) (eq 2).



7 **8** (2)

Similarly, the bisdithiane **9**, prepared from 2,5-dimethoxytetrahydrofuran, gave the cycloheptanedione derivative **10** in 65% yield (eq 3). In order to illustrate the feasibility of this method for the synthesis of cyclic diketones, the bisdithiane **10** was converted to cycloheptane-1,4-dione under mild conditions by mercuric chloride-promoted hydrolysis in the presence of mercuric oxide (to limit the acidity of the reaction mixture).



9 **10** (3)

The application of dithiane-derived anions to the formation of small and common-size rings would appear from the present results to have considerable generality and potential. It seems reasonable to expect that the method can be used for the construction of more highly substituted rings, and also of certain fused ring systems. It is obvious that the scope of this ring closure will be limited to cases where there are no interfering reactive functional groups such as carbonyl or hydroxyl in the substrate for cyclization. Even in the case of simple compounds such as cyclobutanone or cycloheptane-1,4-dione, the synthetic route described herein would seem to be efficient enough to be of practical value.

Experimental Section

Melting points were determined using a Büchi melting point apparatus and are corrected. Infrared spectra were obtained using a Perkin-Elmer 137 Infracord spectrophotometer and ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer. The nmr data were obtained at 60 Mc using a Varian Associates Model A-60 spectrometer and are expressed as shifts downfield from internal tetramethylsilane in parts per million. The mass spectra were taken with an Associated Electrical Industries Ltd. Model MS 9 mass spectrometer. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and A. Bernhardt, Mülheim, Germany.

Tetrahydrofuran was purified just prior to use by distillation from lithium aluminum hydride. Pyridine was dried by distillation from calcium hydride.

1,3-Dithiane.—In a 5-l. three-necked, round-bottomed flask with ground-glass fittings was placed a mixture of 180 ml of boron trifluoride etherate, 360 ml of glacial acetic acid, and 600 ml of chloroform. The flask was equipped with a spiral reflux condenser, an efficient mechanical stirrer, and a dropping funnel. The chloroform solution in the flask was heated and maintained

TABLE I

2-(ω-CHLOROALKYL)-1,3-DITHIANES

Product	Yield, %	Bp, °C (mm)	Formula	Calcd, % C	H	Cl	S	Found, % C	H	Cl	S
1, n = 3	83	105 (0.2)	$C_7H_{13}ClS_2$	42.73	6.66	18.02	32.59	42.85	6.57	17.95	32.47
1, n = 4	60	110 (0.17)	$C_8H_{15}ClS_2$	45.58	7.17	16.82	30.42	45.81	7.32	16.89	30.19
1, n = 5	79	116 (0.04)	$C_9H_{17}ClS_2$	48.08	7.62	15.77	28.53	48.07	7.63	15.71	28.29
1, n = 6	71	121 (0.07)	$C_{10}H_{19}ClS_2$	50.29	8.02	14.84	26.85	50.14	8.16	15.04	26.62
1, n = 7	73	148 (0.35)	$C_{11}H_{21}ClS_2$	52.25	8.37	14.02	25.36	52.43	8.32	13.95	25.22

at reflux with vigorous stirring, and a solution of 150 ml of 1,3-propanedithiol (1.5 moles) and 145 ml of methylal (1.65 moles) in 2.25 l. of chloroform was added at a constant rate over 8 hr. The mixture was allowed to cool to room temperature and washed successively with four 400-ml portions of water, twice with 600 ml of 10% aqueous potassium hydroxide, and twice with 400-ml portions of water. The chloroform solution thus obtained was dried over potassium carbonate and concentrated in a 500-ml, round-bottomed flask under reduced pressure using a rotating flask evaporator. The residue, which crystallized upon cooling to room temperature, was dissolved in 300 ml of methanol by heating to the boiling point. The hot solution was filtered rapidly, using a prewarmed funnel, allowed to cool slowly to room temperature, and then kept overnight at −20°. The colorless crystals were collected by filtration through a prechilled Büchner funnel, washed with cold methanol (−20°), and dried under reduced pressure. The yield of dry product, mp 52–53°, was 130–140 g. Solvent was removed from the mother liquor, and the residue was recrystallized as described to furnish an additional 10–15 g. A purer sample can be prepared by subsequent sublimation of the recrystallized product at 0.1–0.5 mm (45–48° bath temperature). The yield of pure product so obtained was 138–152 g (77–84%), mp 53–54°.[3]

Preparation of 2-(ω-Chloroalkyl)-1,3-dithianes.—Most of the α,ω-dichloroalkanes were obtained commercially. The C_4, C_5, and C_7 members of the series $I(CH_2)_nCl$ were obtained by selective iodide chloride exchange;[4] the C_6 member was synthesized from 6-chlorohexan-1-ol by a recently described method[5] as follows. To a solution of 31.8 g of *o*-phenylene phosphochloridite and 15 ml of pyridine in 170 ml of ether at 0° was added 25 g of 6-chlorohexan-1-ol in 120 ml of ether with cooling (ice bath) over 35 min. After 17 hr at 25° the mixture was filtered, and the filtrate was concentrated to remove ether. The residue was taken up in 400 ml of methylene chloride and added at 25° over 20 min to a mixture of 42.5 g of iodine and 800 ml of methylene chloride. After 17 hr the red solution was washed twice successively with 7% potassium hydroxide (200 ml), water, concentrated hydrochloric acid (50 ml), sodium bisulfite (50 ml, 5%), and sodium bicarbonate and then dried. Distillation afforded 35.5 g (79%) of 1-chloro-6-iodohexane, bp 65° (0.3 mm), $n^{22}D$ 1.5231 (lit.[4] $n^{22}D$ 1.5248).

Method A. From 1-Chloro-ω-bromo- or 1-Chloro-ω-iodo-*n*-alkanes.—To a 0.1 to 0.3-*M* solution of 2-lithio-1,3-dithiane[2a] stirred at −50° was added an equimolar amount of pure, neat dihalide under nitrogen. After a short time between −50 and −20° and a further 12 hr at −20°, a few milliliters of water were added, and the tetrahydrofuran was removed *in vacuo*. Addition of water and extraction with pentane followed by alkaline washing of the organic extract, drying (K_2CO_3), removal of solvent, and distillation under reduced pressure afforded the 2-(ω-chloroalkyl)-1,3-dithianes indicated in Table I. The nmr spectra of the chloroalkyldithianes **1** exhibited uniformly a triplet (1 H) due to the proton at C_2 of the dithiane ring at *ca.* 4.0 (J = 6–7 cps) and a triplet (2 H) due to the methylene attached to chlorine at 3.6–3.5 ppm (J = 6–7 cps).

Method B. From 1,ω-Dichloro-*n*-alkanes.—A solution containing 0.025 mole of 2-lithio-1,3-dithiane[2a] in 36 ml of tetrahydrofuran and 16 ml of *n*-hexane under nitrogen at −35° was stirred and treated with 0.065 mole of neat, pure dichloride. After a reaction time of 24 hr at −20° and 24 hr at 0°, a few milliliters of water were added, and most of the tetrahydrofuran was removed under reduced pressure. The resulting 2-(ω-chloroalkyl)-1,3-dithiane was isolated as described in the preceding section. Unreacted dichloride could easily be removed by distillation.

2-(β-Chloroethyl)-1,3-dithiane (3, X = Cl). A. From β-Chloropropionaldehyde Diethyl Acetal.—Dry hydrogen chloride was bubbled through a solution of 31.2 g (0.187 mole) of the acetal and 18.7 ml (0.185 mole) of 1,3-propanedithiol in 500 ml of chloroform for 10 min. After 1.5 hr the mixture was poured into 200 ml of water. The combined organic layers obtained by extracting the aqueous phase three times with chloroform were washed three times each with 150 ml of 10% potassium hydroxide and water, and dried over potassium carbonate. After evaporation of the solvent the residual oil was distilled to give 22.7 g (66.4%) of **3**, X = Cl, as a colorless liquid, bp 84.5–86° (0.2 mm), $n^{20}D$ 1.5684. The product contained small amounts of an OEt-containing impurity (nmr analysis) which could not be removed by fractional distillation or by partial hydrolysis. An analytical sample was obtained by chromatography through silica gel: $n^{20}D$ 1.5749; infrared spectrum (neat), 7.04, 7.50, 7.68, 7.86, 7.92, 8.07, 8.36, 10.62, 11.01 (dithiane band), 11.52, 12.55, 12.98, and 14.03 μ; nmr spectrum (CCl_4), a methine proton on the dithiane ring as a triplet (J = 7 cps) at 4.19 and methylene protons attached to chlorine as a triplet (J = 7 cps) at 3.68 ppm.

Anal. Calcd for $C_6H_{11}ClS_2$: C, 39.43; H, 6.07; Cl, 19.40; S, 35.10. Found: C, 39.33; H, 6.18; Cl, 19.43; S, 34.95.

B. From 2-(β-Hydroxyethyl)-1,3-dithiane (3, X = OH).—From 16.00 g (0.050 mole) of the tosylate **3**, X = OTs (see below), stirred for 6 days at 30° in 100 ml of dimethylformamide saturated with dry lithium chloride, there was obtained 7.589 g of slightly yellow **3**, X = Cl (82.6%). The infrared spectrum was identical with that of the analytical sample obtained as described above. Alternatively, to 291 mg of the hydroxy compound **3**, X = OH, in 4 ml of methylene chloride, stirred at 0°, was added 0.11 ml of thionyl chloride. The bath was removed after 5 min and stirring was continued at 25° for 2 hr. The solvent and excess thionyl chloride were removed on a rotating flask evaporator (30° at 20 mm). After addition of 5 ml of a saturated solution of dry lithium chloride in dimethylformamide, stirring was continued for 15.5 hr. Water was added, and the product was extracted with three 15-ml portions of pentane. Washing with potassium hydroxide and water, drying over potassium carbonate, and evaporating the solvent furnished 202 mg (62.6%) of colorless chloride, the infrared spectrum of which was superimposable with that of authentic material.

2-(β-Hydroxyethyl)-1,3-dithiane (3, X = OH).—From 6.66 mmoles of the 2-lithio-1,3-dithiane[2a] and 0.33 ml (295 mg, 6.70 mmoles) of neat ethylene oxide (added with a prechilled hypodermic syringe) was obtained after isolation in the usual way 0.969 g (88.7%) of crude **3**, X = OH, after a reaction time of 20 hr. Distillation at 100° (0.03 mm) gave 816 mg (74.7%) of a viscous colorless liquid: bp 100° (0.03 mm); $n^{20}D$ 1.5788; infrared spectrum (neat), strong OH absorption at 2.88 and a dithiane band at 10.94 μ; nmr spectrum (CCl_4), methylene attached to oxygen as a triplet at 3.72 (J = 6 cps), methine at C_2 of the dithiane as a triplet at 4.21 (J = 7 cps), and OH as a singlet at 3.98 ppm. The reaction was also carried out in an 0.08-mole scale, yielding 95.5% of crude **3**, X = OH.

Anal. Calcd for $C_6H_{12}OS_2$: C, 43.90; H, 7.37; O, 9.74; S, 38.99. Found: C, 44.10; H, 7.22; O, 9.94; S, 38.85.

The *p*-toluenesulfonate **3**, X = OTs, was prepared from **3**, X = OH, using *ca.* 20% molar excess of *p*-toluenesulfonyl chloride in dry pyridine (2 ml/mmole of **3**, X = OH) at 0° for 48 hr and isolated by addition of a small amount of water, pouring onto ice, and extraction after a 30-min period using methylene chloride. The extracts were freed of pyridine by washing with 5% aqueous hydrochloric acid followed by water. Drying and removal of solvent *in vacuo* furnished *p*-toluenesulfonate of ade-

(3) 1,3-Dithiane has been reported previously several times but details of the preparations have not been described; see, for example, W. Autenrieth and K. Wolff, *Ber.*, **32**, 1375 (1899), and D. T. Gibson, *J. Chem. Soc.*, 12 (1930).

(4) R. H. Raphael and F. Sondheimer, *ibid.*, 2100 (1950).

(5) E. J. Corey and J. E. Anderson, *J. Org. Chem.*, in press.

TABLE II

PRODUCTS FROM CYCLIZATION OF 2-(ω-CHLOROALKYL)-1,3-DITHIANES

Product	Yield, %[a]	Bp, °C (mm)	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2a	61	57.5–57.8[b]	$C_6H_{10}S_2$	49.31	6.90	43.79	49.39	6.90	43.72
4	57	75[c] (0.3)	$C_7H_{12}S_2$	52.49	7.55	39.96	52.49	7.58	39.84
5	84	95[c] (0.05)	$C_{10}H_{16}S_2$	59.98	8.05	31.97	60.04	7.94	31.81
2b	84	65 (0.4)	$C_7H_{12}S_2$	52.49	7.55	39.96	52.41	7.51	40.00
2c	87	66 (0.1)	$C_8H_{14}S_2$	55.16	8.10	36.74	55.19	8.01	36.63
2d	71	40.6–41.0[b]	$C_9H_{16}S_2$	57.43	8.57	34.00	57.39	8.38	33.94
2e	68	106[c] (0.06)	$C_{10}H_{18}S_2$	59.38	8.97	31.65	59.37	8.75	31.60

[a] After purification; analytical yields of crude products were 80–100%. [b] Melting point, recrystallized from methanol and sublimed. [c] Bath temperature.

quate purity for the cyclization to form **2a** or for conversion to the chloride **3**, X = Cl.

2-(β-Hydroxypropyl)-1,3-dithiane was obtained after a reaction time of 16 hr as a crude product (3.36 g, 99.8%) (as described above for **3**, X = OH) from 18.95 mmoles of 2-lithio-1,3-dithiane and 1.325 ml (1.10 g, 19.0 mmoles) of neat propylene oxide. Distillation at 100° (0.025 mm) gave 2.460 g (73.0%): $n^{20}D$ 1.5626; infrared spectrum (neat), OH at 2.89 and a dithiane band at 11.00 μ; nmr spectrum (CCl_4), OH as a singlet at 3.30, CH at C_2 of the dithiane as a triplet at 4.06 (J = 6 cps), and CH_3 as a doublet at 1.20 ppm (J = 6.2 cps).

Anal. Calcd for $C_7H_{14}OS_2$: C, 47.18; H, 7.92; S, 35.92. Found: C, 47.10; H, 7.94; S, 35.81.

The *p*-toluenesulfonate, prepared as described above for **3**, X = OH, was recrystallized from pentane at −20°, mp 74.8–75.5°.

Anal. Calcd for $C_{14}H_{20}O_3S_3$: C, 50.60; H, 6.07; S, 28.89. Found: C, 51.05; H, 6.30; S, 28.61.

1,3-Propylene Dithioacetal of *trans*-2-Hydroxy-1-cyclohexanecarboxaldehyde.—From 23.55 mmoles of 2-lithio-1,3-dithiane and 2.40 ml (2.32 g, 23.60 mmoles) of neat cyclohexene oxide was obtained (using the customary work-up procedure), after a reaction time of 43 hr, 4.835 g (94.3%) of colorless crystals, mp 95.5–98.5°. An analytical sample of the β-hydroxycyclohexyldithiane prepared by two recrystallizations carried out by boiling 1 g of solid in 15 ml of pentane and adding dropwise benzene until a clear solution was obtained, filtering, seeding, and cooling at 0°, was obtained as colorless massive prisms: mp 99.0–100.2°; infrared spectrum (CCl_4), OH at 2.70 and 2.82 and a dithiane band at 10.96 μ.

Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.03; H, 8.31; S, 29.33. Found: C, 54.96; H, 8.19; S, 29.35.

The corresponding *p*-toluenesulfonate was prepared from 2.316 g (10.6 mmoles) of the hydroxypropyldithiane and 2.431 g (12.7 mmoles, 20% excess) of *p*-toluenesulfonyl chloride with a reaction time of 47 hr. Recrystallization in two crops furnished 3.395 g (85.8%) of colorless fine needles: mp 133–135° (dec to a red oil, 1°/min heating rate); infrared spectrum ($CHCl_3$), 3.37, 3.49, 6.26, 7.37, 8.50, 9.11, 10.36, 10.49, 10.85, 11.00, 11.10, and 11.38 μ; nmr spectrum ($CDCl_3$), aromatic protons as two doublets (J = 8.2 cps) at 7.85 and 7.31, methine proton at C_2 of the dithiane system as a doublet (J = 2.1 cps) at 4.20, methyl protons as a singlet at 2.43, and HC–O proton as a multiplet at 4.62 ppm.

Anal. Calcd for $C_{17}H_{24}O_3S_3$: C, 54.83; H, 6.50; S, 25.78. Found: C, 55.05; H, 6.52; S, 25.66.

General Procedure for the Preparation of 1,3-Dithiane Derivatives of Cyclic Monoketones from 2-(ω-Chloroalkyl)-1,3-dithianes and from *p*-Toluenesulfonates of 2-(β-Hydroxyalkyl)-1,3-dithianes. A. From Chlorides.—A 0.10–0.15 M solution of the chloroalkyldithiane (0.02–0.05 M if a 7-membered ring was to be formed) in freshly distilled dry tetrahydrofuran was stirred under nitrogen with cooling to −70° in a Dry Ice–acetone bath and combined with 1.05 equiv of *n*-butyllithium solution in *n*-hexane (Foote Mineral Co.). The flask was sealed under nitrogen and stored for 24 hr each, first at −20° and then at 0°. The reaction was worked up as described for the preparation of the 2-(ω-chloroalkyl)-1,3-dithianes. Evaporation of the pentane furnished the crude products.

B. From 1,3-Dithiane without Isolation of Intermediates.—To a 0.2–0.5 M solution of 2-lithio-1,3-dithiane under nitrogen was added at −50° an equimolar amount of pure, neat 1-chloro-ω-iodo- or 1-chloro-ω-bromo-*n*-alkane. The mixture was kept at −20° for 12 hr and cooled to −70° (lithium iodide usually precipitates from the stirred solution upon cooling). Tetrahydrofuran was added to obtain a *ca.* 0.15 M solution, and 1.10 equiv of *n*-butyllithium was injected all at once; then the product was isolated by the above procedure.

C. From Tosylates.—A 0.1 M solution of the tosylate in tetrahydrofuran was stirred under nitrogen in a −70° bath, and 1.1 equiv of phenyllithium in ether (LiBr saturated) or of *n*-butyllithium was added. The temperature was allowed to rise to −20° within 1.0 hr. The flask was sealed and kept for 12–15 hr each, first at −20° and then at 0°. The deep-colored solutions were poured into a fourfold volume of water. The pH of the aqueous layer was brought to 5 with hydrochloric acid. After extraction with pentane the isolation procedure described above for the 2-(ω-chloroalkyl)-1,3-dithianes was followed.

Table II presents specific data on the preparation of the individual cyclization products **2a–e**, **4**, and **5**. In each case the infrared and nmr spectra were consistent with the assigned structures. In addition, **2b**, **2d**, and **2e** were synthesized independently from 1,3-propanedithiol and cyclobutanone, cyclopentanone, and cycloheptanone, respectively, and samples prepared by the two methods were shown to be identical by spectral comparison. To illustrate the conversion of these 1,3-propylene dithioketal derivatives to ketones, **2b** was converted on a small scale to cyclobutanone as described below.

Cyclobutanone.—A mixture of 2.401 g (15.0 mmoles) of the cyclobutanone derivative, **1b**, 80 ml of ethylene glycol, 2 ml of concentrated hydrochloric acid, 10 ml of water, and 9.0 g (33 mmoles) of mercuric chloride was stirred vigorously for 3 hr at 85–90°. A slow stream of dry nitrogen was passed through the solution using a hypodermic syringe needle. After leaving the reaction vessel through a 5-cm length of polyethylene tubing, the nitrogen passed a trap attached reversely and cooled at Dry Ice–acetone temperature. The product which is solid at that temperature separated in long needles. Anhydrous sodium sulfate (10 g) was added into the trap, and the ketone was extracted with ten 25-ml portions of methylene chloride, which was removed by fractional distillation through a 60-cm glass helix-packed, vacuum-insulated, and silvered column. The residue was distilled in a microdistillation apparatus to yield 630 mg (60%) of cyclobutanone; the infrared spectrum (neat, C=O at 5.59 μ) and nmr spectrum (CCl_4, degenerate pentet at 1.93 (J = 8 cps) and triplet at 3.01 ppm (J = 8 cps), ratio 1:2) were superimposable with the spectra of an authentic sample (Aldrich Chemical Co.) except that there was a small peak in the nmr spectrum at 3.80 ppm, due to a small amount (*ca.* 5%) of the dioxolane derivative of cyclobutanone present. The use of diethylene glycol as solvent and isolation of cyclobutanone by direct distillation from the Dry–Ice trap after addition of sodium sulfate could probably lead to higher yield and purity of cyclobutanone. For higher boiling ketones, extraction with methylene chloride, pentane, or Freon 11 should be adequate.

Bis-1,3-propylene Dithioacetal of Malonaldehyde (7).—To a solution containing 53.0 mmole of 2-lithio-1,3-dithiane under nitrogen at −20° was added 8.20 ml (10.5 g, 53.3 mmoles) of bromoacetaldehyde diethyl acetal. The flask was stored at −20° for 20 hr, then put on a rotary evaporator. Removal of the solvents resulted in a slightly brown mixture of lithium bromide and an oil to which was added 350 ml of chloroform. To the stirred slurry was added 5.50 ml (54 mmoles) of 1,3-propanedithiol, and a rapid stream of hydrogen chloride was passed through for 10 min. Stirring was continued for 16 hr. Three washings with water, two with 7% potassium hydroxide, and two

additional washings with water, drying over potassium carbonate, and evaporating the solvent led to the crude oily crystalline product. Methanol (100 ml) was added and brought to boiling; chloroform was added dropwise until complete solution had taken place, and 1 g of potassium carbonate and 1.5 g of charcoal were introduced carefully into the boiling solution. Filtering and cooling gave 7.503 g (56.3%) of colorless product. From the mother liquor an additional 0.852 g of pure **7** could be obtained (total yield, 62%): mp 113.0–114.5°; infrared spectrum ($CHCl_3$) 3.30, 3.40, 3.52, 7.05, 7.84, 8.07, 8.53, 8.9, 10.0, 10.65, 11.52 μ; nmr spectrum ($CDCl_3$), methine protons at C_2 of the dithiane system as a triplet (J = 7.5 cps) at 4.25 and methylene protons as a triplet (J = 7.5 cps) at 2.21 ppm.

Anal. Calcd for $C_9H_{16}S_4$: C, 42.86; H, 6.39; S, 50.75. Found: C, 42.81; H, 6.41; S, 50.67.

Bis-1,3-propylene Dithioacetal of Succinaldehyde (9).—2,5-Dimethoxytetrahydrofuran (20.0 g, 0.151 mole), 31.0 ml (0.305 mole) of 1,3-propanedithiol, and 300 ml of chloroform were mixed and treated with a rapid stream of gaseous hydrogen chloride for 10 min (considerable evolution of heat). The mixture was allowed to cool and stand at room temperature for 3.5 hr and at 0° for 14 hr. Work-up as described for the malonaldehyde derivative **7** gave 42.00 g of crude product which yielded after purification 33.63 g (83.0%) of colorless crystalline **9**, mp 132–135°, in two crops. The analytical sample was obtained by two further recrystallizations from chloroform–methanol: mp 134.7–135.2°; infrared spectrum (CCl_4), 3.45, 7.08, 7.88, and 10.96 μ (dithiane band); nmr spectrum ($CDCl_3$), CH at C_2 of the dithiane ring as complex signal at 4.04, methylenes attached to the sulfur as a multiplet centered at 2.85, and all other protons as multiplet centered at 2.0 ppm, ratio 1:4:4.

Anal. Calcd for $C_{10}H_{18}S_4$: C, 45.11; H, 6.81; S, 48.08. Found: C, 45.17; H, 6.80; S, 47.85.

The bisdithioacetal **9** was also prepared by alkylation of 2-lithio-1,3-dithiane with β-chloroacetaldehyde diethyl acetal and subsequent reaction of the intermediate acetal dithioacetal with 1,3-propanedithiol (as above for **7**).

Bis-1,3-propane Dithioketal of 1,3-Cyclohexanedione (8).—A solution of 4.293 g (17.03 mmoles) of twice recrystallized **7** in 180 ml of dry tetrahydrofuran was stirred at −30° and combined with 18.58 mmoles of *n*-butyllithium. After 4 hr at −20°, 3.580 g (17.50 mmoles) of neat 1,3-chloroiodopropane was added. The temperature was kept for 90 min each at −20° and at 0°. The mixture was cooled in a −70° bath with stirring and treated with 19.20 mmoles of *n*-butyllithium. After storage at −20° for 23 hr and at 0° for 79 hr, an almost black solution had been formed which turned to a light orange-red upon addition of a few milliliters of water. Most of the solvent was removed, and water was added to the residue. The combined solution from three extractions with 70-ml portions of methylene chloride was washed once with saturated sodium chloride, once with 7% potassium hydroxide, and three times with water. The dried (potassium carbonate) solution furnished 4.511 g of crude product as a viscous red oil after evaporation of the solvent. The material was purified by chromatographic filtration as follows. A solution in 4 ml of benzene was added to a 30-cm column containing 18 g of silica gel in petroleum ether. Elution with 1 l. of 25% ether in petroleum ether (40–60°) gave 2.405 g (48%) of colorless crystals after evaporation of the solvent: mp 124.9–125.2° (short needles from methanol using charcoal); infrared spectrum ($CHCl_3$), 3.31, 3.36, 3.50, 6.90, 6.98, 7.02, 7.86, 9.03, 9.98, 10.74, 10.92, and 11.03 μ; nmr spectrum ($CDCl_3$), protons at the 4 and 6 positions of the dithiane system as a broad multiplet centered at 2.87, CH_2 protons at the 2 position of the cyclohexane ring as a sharp singlet at 2.60, and all other protons as a multiplet centered at 2.0 ppm, ratio 4:1:5. The mass spectrum showed a molecular ion peak at m/e 292.

Anal. Calcd for $C_{12}H_{20}S_4$: C, 49.31; H. 6.90; S, 43.79. Found: C, 49.33; H, 7.03; S, 43.69.

Bis-1,3-propane Dithioketal of 1,4-Cycloheptanedione (10).—A solution of 3.064 g (11.52 mmoles) of twice recrystallized **9** in 300 ml of tetrahydrofuran was treated at −30° with 12.80 mmoles of *n*-butyllithium. After 4 hr at −20°, 2.460 g (12.02 mmoles) of neat 1,3-chloroiodopropane was added. The procedure described for **8** was followed, using 13.1 mmoles of *n*-butyllithium for the cyclization step (concentration *ca.* 0.035 mole/l.). The crude crystalline product (2.888 g, 84%) gave 2.257 g (65%) of colorless crystals of **10** by chromatographic filtration carried out as described above for **8**. Recrystallization from methanol using charcoal gave the analytical sample of **10** as needle-shaped plates: mp 123.3–123.7°; nmr spectrum ($CDCl_3$), protons at the 4 and 6 positions of the dithiane rings as a multiplet centered at 2.83, CH_2 protons at the 2 and 3 positions of the seven-membered ring as a sharp singlet at 2.27, and all other protons as a multiplet centered at 2.0 ppm, ratio 4:2:5. The molecular ion appeared in the mass spectrum at m/e 306.

Anal. Calcd for $C_{13}H_{22}S_4$: C, 50.97; H, 7.24; S, 41.79. Found: C, 50.98; H, 7.33; S, 41.74.

Cycloheptane-1,4-dione.—A mixture of 600 mg (1.96 mmoles) of the diketone derivative **10**, 2.28 g (8.40 mmoles) of mercuric chloride, 706 mg (3.25 mmoles) of mercuric oxide, 3 ml of water, and 50 ml of reagent grade methanol was heated at reflux for 4 hr with rapid stirring under an atmosphere of nitrogen. The cold mixture was filtered, and residue was washed with methylene chloride. The filtrate was diluted with a threefold volume of water and extracted three times with 30 ml of methylene chloride. The combined methylene chloride solutions were washed twice with ammonium chloride solution and dried over magnesium sulfate. Evaporation of the solvent at 35° (30 mm) gave 232 mg (94%) of a colorless, clear liquid, the infrared spectrum of which was identical with that of the sample further purified. Microdistillation (95–100° bath at 0.9 mm) furnished 152 mg (61.6%) of pure diketone, $n^{20}D$ 1.4818 (lit.[6,7] bp 118–119° (2 mm), 90° (0.8 mm); $n^{20}D$ 1.4842). The infrared spectrum (CCl_4) showed carbonyl absorption at 5.85 μ. The nmr spectrum (CCl_4) showed the pattern expected: two-proton multiplet centered at 2.0, four-proton triplet (J = 5.5 cps) with broadened peaks at 2.64, and very sharp four-proton singlet at 2.56 ppm.

The brick-red bis-2,4-dinitrophenylhydrazone prepared from cycloheptan-1,4-dione after recrystallization from pyridine had mp 238–239° (with decomposition) when inserted in the bath at 230° with a heating rate of 1°/min.[8]

Bicyclic Sulfonium Salt 6a.—To a solution of 3.553 g of propane-1,3-dibromide (17.6 mmoles) dissolved in 25 ml of tetrahydrofuran and stirred at 0° under N_2 was added a solution of 2-lithio-1,3-dithiane (containing 18.0 mmoles of anion) over 25 min. The flask was sealed under N_2 pressure and stored at 0° for 24 hr and at 28° for 2 hr. Since it was not expected that a sulfonium salt might be formed, the usual work-up procedure for alkylation reactions was applied, using $CHCl_3$ as a solvent. The colorless chloroform solution (200 ml) obtained after washing was dried over potassium carbonate for 15 hr at 25°. Evaporation of the solvent furnished 3.465 g of colorless crystals; most of this material was water soluble. The solution in 50 ml of water was washed with benzene and the water was evaporated at the rotary evaporator (50° at 18 mm); a very viscous clear oil was obtained and dried in a desiccator over P_2O_5 at 0.3 mm to yield 2.2 g (52%) of dry, colorless, extremely hygroscopic crystals. A small amount was dissolved in boiling absolute ethanol and filtered. The filtrate was treated with ether until cloudy and slowly cooled to −20°. Well-formed, heavy rods were obtained, mp 140.5–141.0° (with decomposition, heating rate 1°/min, sealed melting point tube).

Anal. Calcd for $C_7H_{13}BrS_2$: C, 34.85; H, 5.43; Br, 33.13; S, 26.59. Found: C, 35.07; H, 5.55; Br, 33.07; S, 26.50.

Bicyclic Sulfonium Salt 6b.—From 7.523 g of butane-1,4-dibromide (34.9 mmoles) and an anion solution containing 17.9 mmoles of 2-lithio-1,3-dithiane, 1.423 g of dry, crystalline sulfonium bromide was obtained, following exactly the same procedure described above. A sample, recrystallized from ethanol–ether, was analyzed.

Anal. Calcd for $C_8H_{15}BrS_2$: C, 37.64; H, 5.92; Br, 31.31; S, 25.12. Found: C, 37.68; H, 6.01; Br, 31.36; S, 24.93.

Registry No.—**1** (n = 3), 14947-43-4; **1** (n = 4), 15077-15-3; **1** (n = 5), 14947-44-5; **1** (n = 6), 14947-45-6; **1** (n = 7), 14947-46-7; **2a**, 14947-47-8; **2b**, 15077-16-4; **2c**, 15077-17-5; **2d**, 180-96-1; **2e**, 15077-18-6; **3** (X = Cl), 15077-19-7; **3** (X = OH), 14947-48-9; **4**, 14947-49-0; **5**, 15077-20-0; **6a**, 5849-14-9; **6b**, 5849-15-0; **7**, 14947-51-4; **8**, 14947-52-5; **9**, 14947-53-6; **10**, 14950-

(6) J. Rigaudy and P. Courtot, *Compt. Rend.*, **248**, 3016 (1959).
(7) W. von E. Doering and A. A.-R. Sayigh, *J. Org. Chem.*, **26**, 1365 (1961).
(8) See A. C. Cope, Th. A. Liss, and G. W. Wood, *J. Am. Chem. Soc.*, **79**, 6287 (1957).

47-1; 1,3-dithiane, 505-23-7; 2-(β-hydroxypropyl)-1,3-dithiane, 14950-49-3; 2-(β-hydroxypropyl)-1,3-dithiane *p*-toluenesulfonate, 14950-42-6; 1,3-propylene dithioacetal of *trans*-2-hydroxy-1-cyclohexanecarboxaldehyde, 14950-43-7; 1,3-propylene dithioacetal of *trans*-2-hydroxy-1-cyclohexanecarboxaldehyde *p*-toluenesulfonate, 14950-44-8; cyclobutanone, 1191-95-3; cycloheptane-1,4-dione, 14950-46-0.

Acknowledgment.—We are indebted to the National Science Foundation and the National Institutes of Health for financial support of this research.

Mass Spectrometry in Structural and Stereochemical Problems. CXLVI.[1] Mass Spectrometric Fragmentations Typical of Sterols with Unsaturated Side Chains[2]

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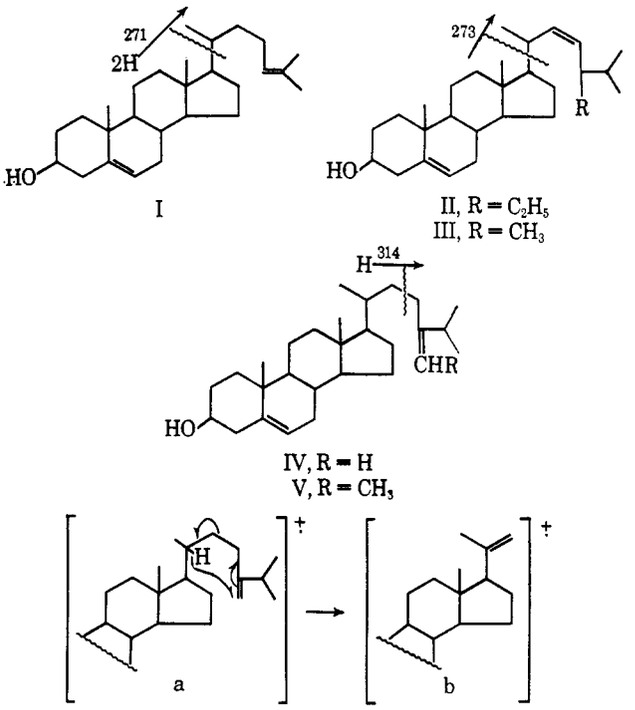
Received August 10, 1967

The characteristic mass spectral features associated with the usual saturated side chain of sterols are drastically altered when double bonds are introduced into the side chain. One of the most diagnostic and mechanistically intriguing fragmentations of such unsaturated sterols involves the loss of the entire C-17 substituent together with the rearrangement of two hydrogen atoms. Attention is drawn to the utility of such mass spectral decompositions in structure elucidation of unknown sterols and the nature of the fragmentation processes has been clarified through the use of deuterium-labeled steroids. In that connection several syntheses of Δ^{22}- and Δ^{24}-steroidal olefins were developed.

The mass spectrometric fragmentations of steroids, initiated either by various functional groups or inherent in the steroidal skeleton have been the subject of considerable study[4] in our laboratory both with regard to their use as a structural tool and the elucidation of their mechanism. During the examination of the mass spectra of a number of naturally occurring sterols it became apparent that a diagnostically important and mechanistically interesting cleavage was associated with the presence of a double bond in the side chain. Thus an intense peak at *m/e* 271 appears in the mass spectrum of desmosterol (I), this fragment corresponding to the loss of the side chain together with two hydrogen atoms from the steroid nucleus. Stigmasterol (II) and a number of 6,7-dihydroergosterol (III) derivatives show a similar peak though of reduced intensity owing to the competing allylic cleavage of the 17–20 bond giving an ion of mass 273. Similarly 24-methylenecholesterol (IV) and fucosterol (V) show an *m/e* 271 peak although of low intensity compared with the strong peak at *m/e* 314 which dominates the mass spectra of these compounds. This latter fragment must arise by cleavage of the 22–23 bond together with a one hydrogen transfer from the charge retaining moiety. Mechanistically this decomposition may be rationalized by a "McLafferty" type of rearrangement (a → b), the transferred hydrogen originating from C-20.



Since the outset of our investigation both of the above fragmentations have been noted by a number of workers,[5] but, although the "McLafferty" type of mechanism has been proposed to explain the genesis of the *m/e* 314 peak or its equivalent, no explanation has been forthcoming regarding the formation of the important fragment of mass 271. In view of the generality of this fragmentation, its diagnostic utility for the structural elucidation of new sterols,

(1) Paper CXLV: W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 6167 (1967).

(2) Financial assistance by the National Institutes of Health (Grants No. AM-04257 and CA-07195) of the U. S. Public Health Service is gratefully acknowledged.

(3) Postdoctoral Research Fellow, 1965–1967.

(4) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964; (b) R. T. LaLonde, L. Tökés, and C. Djerassi, *J. Org. Chem.*, **32**, 1012 (1967); (c) R. T. LaLonde, L. Tökés, and C. Djerassi, *ibid.*, **32**, 1020 (1967); (d) L. Tökés, G. Jones, and C. Djerassi, in preparation.

(5) (a) P. Eneroth, K. Hellström, and R. Ryhage, *Steroids*, **6**, 707 (1965); (b) J. Bergman, B. O. Lindgren, and C. M. Svahn, *Acta Chem. Scand.*, **19**, 1661 (1965); (c) B. A. Knights, *Phytochemistry*, **4**, 857 (1965); (d) B. A. Knights and W. Laurie, *ibid.*, **6**, 407 (1967); (e) P. Benveniste, L. Hirth, and G. Ourisson, *ibid.*, **5**, 31 (1966); (f) W. Sucrow, *Chem. Ber.*, **99**, 3559 (1966); (g) N. Ikekawa, K. Tsuda, and W. Morisaki, *Chem. Ind.* (London), 1179 (1966); (h) P. J. Flanagan and J. B. Thomson, *Steroids*, **9**, 601 (1967); (i) R. T. Aplin and G. M. Hornby, *J. Chem. Soc., Sect. B*, 1078 (1966); (j) B. A. Knights, *J. Gas Chromatog.*, **5**, 273 (1967); (k) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).