g.-atom) at a temperature of 100–130°, and under a nitrogen atmosphere. When solution of the sodium was complete, 1-bromo-2-ethoxyethene [prepared according to the method of Nazarov and co-workers[10] as modified by Wasserman[11] by the use of a light petroleum ether (b.p. 60–71°) solvent and a −40° reaction temperature in the vinyl ether bromination step, 76.5 g., 0.50 mole] was added dropwise to the above mixture over a 50-min. period, at 130–140° with rapid stirring and under a nitrogen atmosphere. Stirring was continued for an additional 2 hr. at 140°, with the precipitation of solid sodium bromide. The reaction mixture was then vacuum filtered to give a yellow filtrate and tan solid sodium bromide. The solid was washed several times with anhydrous ether and oven dried overnight to give 39 g. (76% based on the sodium) of sodium bromide.

The ether washings and yellow filtrate were combined and vacuum distilled to yield 35.0 g. (0.240 mole, 48.0%, b.p. 40.0–40.5° at 0.5 mm.) of ketene ethyl 2-methoxyethyl acetal as the principal product fraction: infrared spectrum, $\nu_{C=C}$ 1640 cm.$^{-1}$ (very strong).

Anal. Calcd. for $C_7H_{14}O_2$: C, 57.5; H, 9.65; mol. wt., 146. Found: C, 57.3; H, 9.89; mol. wt., 148 (Menzies–Wright determination in benzene).

Acknowledgment.—It is a pleasure to acknowledge the laboratory assistance of L. J. Ford, and the analytical services of Johanna Holm and T. R. Lawrence.

(10) I. N. Nazarov, Zh. A. Krasnaya, and V. P. Vinogradov, *Zh. Obsch. Khim.*, **28**, 460 (1958).

(11) H. H. Wasserman, private communication, July 2, 1964.

The Reaction of Diborane with Some Steroidal Thioketals

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Received May 4, 1965

Some time ago the hydrogenolytic reduction of thioketals with hydrazine to the corresponding hydrocarbons was reported.[1] Apparently attempts have not so far been made to effect the same reduction with diborane, and this Note refers to the interesting reduction of some steroidal thioketals with this reagent. The results described here show that this reaction is unexpectedly complicated.

The product of the reaction of excess diborane in ether at 20° with 3-cycloethylenedithiocholest-4-ene (I) was oxidized in the usual way with alkaline hydrogen peroxide to give a mixture of starting material and hydroxy compounds, none of which contained sulfur. Separation by chromatography on alumina gave starting material (44%), 5α-cholestan-4α-ol (II, 13%), and, very surprisingly, 5β-cholestan-3α-ol (III, 32%). 3-Cycloethylenedithio-5α-cholestane did not react with diborane under the same conditions and was recovered unchanged from the reaction sequence. This is in agreement with the reported stability of thio ethers to diborane.[2]

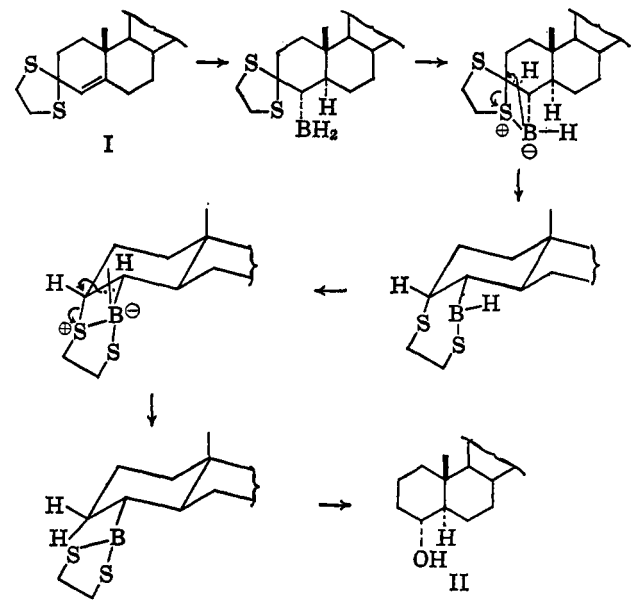
7-Cycloethylenedithio-5α-cholestane was likewise inert to diborane, while 7-cycloethylenedithiocholest-5-ene gave 5α-cholestan-6α-ol (16%) and 5α-cholestan-7β-ol (38%).

(1) V. Georgian, R. Harrison, and N. Gubisch, *J. Am. Chem. Soc.*, **81**, 5834 (1959).

(2) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp. 29, 238.

These results clearly show that diborane cannot be used for the simple hydrogenolytic desulfurization of thioketals, since only those formed from α,β-unsaturated ketones react, and moreover react to give unexpected products. The following mechanisms are suggested for these interesting reactions though at the moment these are admittedly tentative. First, the formation of 5α-cholestan-4α-ol (II) in the reaction of diborane with 3-cycloethylenedithiocholest-4-ene (I) will be considered (Scheme I).

SCHEME I



The initial addition of diborane to the double bond is believed to be followed by boron–sulfur coordination, and then hydride shift from boron to C-3, thereby breaking the $>C-\overset{\oplus}{S}<$ bond. A repetition of this sequence results in complete removal of sulfur from C-3 The boron–sulfur fragment produced in the reaction, in accordance with the known chemistry of boron–sulfur compounds,[3] would not be expected to withstand these alkaline oxidizing conditions. The addition of diborane to the double bond is believed a necessary initial step, since the fact that 3-cycloethylenedithio-5α-cholestane was not desulfurized by diborane seems to exclude the possibility that the 5α-cholestan-4α-ol (II) could have arisen by the addition of diborane to cholest-4-ene produced by a preliminary desulfurization. The stereochemistry of the product (II) is what would be expected from the addition of diborane to the less-hindered α face of the molecule in the anti-Markovnikov sense.[4]

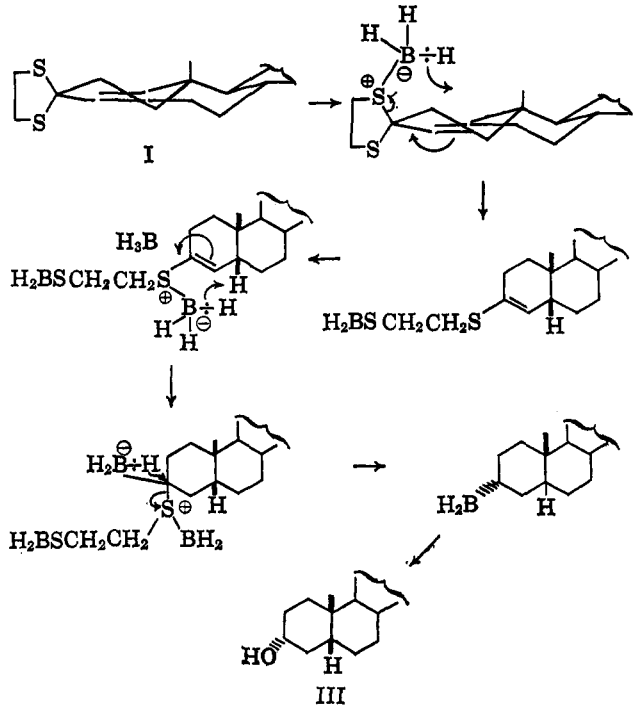
An explanation for the quite surprising formation of 5β-cholestan-3α-ol (III) in this reaction is inevitably more complicated, and is thought to involve as the important preliminary step the formation of a B–S bond instead of a B–C bond (Scheme II).

Several points require comment here. First, though this mechanism satisfactorily accounts for the formation of 5β-cholestan-3α-ol (III), it is not immediately obvious why the formation of a 5α-cholestane deriva-

(3) H. Steinberg, "Organoboron Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 20.

(4) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

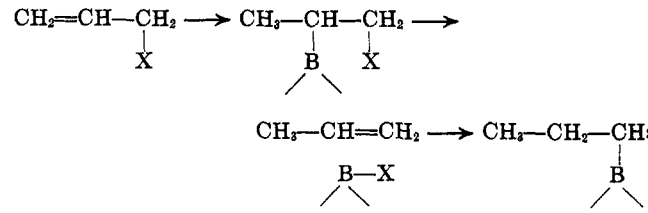
SCHEME II

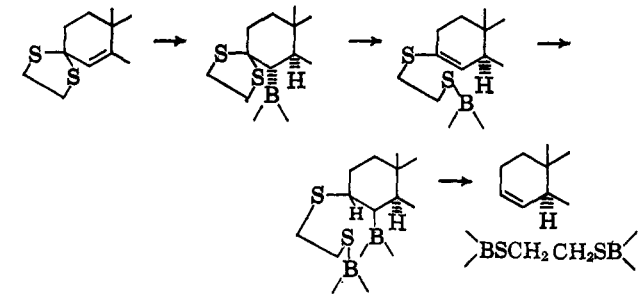


tive, in particular 5α-cholestan-3β-ol, does not occur. Neither 5α-cholestan-3α-ol nor 5α-cholestan-3β-ol was detected among the reaction products. However, the reason for this may be connected with the transition state leading to a 5β-3-ene (that shown) being preferred to that leading to a 5α-3-ene on conformational grounds. It is well-known that the nature of the A/B ring fusion can influence the direction of enolization in 3-keto steroids, and it may be that, conversely, the incipient formation of a 3-ene system such as is involved here determines a 5β configuration at C-5.

The formation of 5α-cholestan-6α-ol in the reaction with 7-cycloethylenedithiocholest-5-ene calls for no special comment, since it is presumably generated by the same mechanism as that suggested above for the formation of 5α-cholestan-4α-ol (II) from 3-cycloethylenedithiocholest-4-ene (I). However, the isolation of 5α-cholestan-7β-ol is more significant. It seems reasonable to suppose that the mechanism of its formation is the same as that suggested above for the formation of 5β-cholestan-3α-ol (III), but in this case a 5β approach of hydride is precluded, since a *cis*-A/B ring fusion requires the 5α-H atom to be axial with respect to ring A and not ring B, and the cyclic transition state necessary for the formation of either 5β-cholestan-7α- or -7β-ol cannot therefore be realized. Such considerations do not affect a 5α approach of hydride, and indeed it was a 5α-cholestane derivative, 5α-cholestan-7β-ol, which was isolated.

These mechanisms obviously require further substantiation. It is of interest to note here a recent paper in which the reaction of diborane with various simple allyl compounds was described.[5] It appears that boron β to a good leaving group is readily eliminable according to the scheme shown, although the nature of the elimination reaction is not fully understood. This might seem to provide an alternative mechanism for the reactions described in this Note. Indeed it can easily account for the formation of 5α-cholestan-4α-ol in the reaction of diborane with 3-cycloethylenedithiocholest-4-ene *via* the olefin 5α-cholest-3-ene as shown. However, it is not possible





to account in this way for the formation of 5β-cholestan-3α-ol in this reaction, since the available evidence indicates that the initial addition of diborane would be to the α face of the molecule (thus cholest-4-ene yields exclusively 5α-cholestan-4α-ol on borohydration[4]).

It might be added, in conclusion, that these results are interesting and surprising in view of the report some time ago that the C–S bonds in allyl methyl sulfide and allyl phenyl sulfide are stable to diborane.[5,6] This suggests that certain quite precise steric conditions for the B–S coordination and hydride shift suggested have to be fulfilled before C–S cleavage occurs, and that these are adequately fulfilled in the case of the steroids mentioned.

Experimental Section[7]

Hydroboration Procedure.—The method followed was that described under method b by Sondheimer and his co-workers.[4]

Oxidation of Organoboranes.—The method used here was also that of Sondheimer and his co-workers.[4]

Preparation of Cyclic Ethylene Thioketals.—These were prepared by allowing the ketone (1 mmole), boron trifluoride etherate (5 mmoles), and excess ethanedithiol to stand in acetic acid at room temperature for 1 hr. The crude product precipitated by the addition of water was chromatographed on alumina (20 g.). Elution with pentane gave the cyclic ethylene thioketal, which was then recrystallized from acetone or acetone–chloroform mixtures. The following compounds were prepared in this way: **3-cycloethylenedithio-5α-cholestane**, m.p. 146–148°, $[\alpha]_D$ +30°, lit.[8] m.p. 146.5–147.5°, $[\alpha]_D$ +32°; **7-cycloethylenedithio-5α-cholestane**, m.p. 142–143° (from acetone), $[\alpha]_D$ −60° (*Anal.* Calcd. for $C_{29}H_{50}S_2$: C, 75.33; H, 10.82; S, 13.85. Found: C, 75.16; H, 10.77; S, 13.52.); **3-cycloethylenedithiocholest-4-ene**, m.p. 117–118°, $[\alpha]_D$ +114°, lit.[8] m.p. 118.5–119.5°, $[\alpha]_D$ + 118.8°; and **7-cycloethylenedithiocholest-5-ene**, m.p. 134–135°, $[\alpha]_D$ −136° (*Anal.* Calcd. for $C_{29}H_{48}S_2$: C, 75.66; H, 10.43; S, 13.91. Found: C, 75.43; H, 10.29; S, 13.58.).

(5) H. C. Brown and O. J. Cope, *J. Am. Chem. Soc.*, **86**, 1801 (1964).

(6) H. C. Brown and K. Murray, *ibid.*, **81**, 4108 (1959).

(7) Melting points are uncorrected. Chromatography was carried out on Peter-Spence Grade H alumina deactivated with 5% of 10% acetic acid. The compounds referred to, where known, were identified with authentic samples by melting point, mixture melting point, and infrared spectra (PE-21 spectrophotometer). Rotations refer to solutions in chloroform at room temperature.

(8) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

3-Cycloethylenedithio-5α-cholestane and 7-cycloethylenedithio-5α-cholestane were recovered unchanged from the hydroboration and subsequent oxidation procedures.

3-Cycloethylenedithiocholest-4-ene (I).—The product from the borohydration of this compound (920 mg., 2 mmoles) and subsequent oxidation of the resulting organoborane was chromatographed on alumina (60 g.). Elution with pentane gave starting material (400 mg.), while elution with pentane–benzene (2:1) gave 5β-cholestan-3α-ol (III, 250 mg., 0.64 mmole, 32%), m.p. 116–117° (from methanol), $[\alpha]_D$ +30°, lit.[9] m.p. 110.5–111.5°, $[\alpha]_D$ +31°. Oxidation with 8 *N* chromic acid in acetone at 0° gave 5β-cholestan-3-one, m.p. 62–63° (from methanol), $[\alpha]_D$ +36°, lit.[9] m.p. 61–62°, $[\alpha]_D$ +36°.

Elution with pentane–benzene (1:1) gave 5α-cholestan-4α-ol (II, 100 mg., 0.26 mmole, 13%), m.p. 188–189° (from methanol–ether), $[\alpha]_D$ +4°, lit.[4] m.p. 188–189°, $[\alpha]_D$ + 3°. Oxidation with 8 *N* chromic acid in acetone at 0° gave 5α-cholestan-4-one, m.p. 97–98° (from methanol), $[\alpha]_D$ +33°, lit.[4] m.p. 99–100°, $[\alpha]_D$ +30°.

7-Cycloethylenedithiocholest-5-ene.—The product from the borohydration of this compound (920 mg., 2 mmoles) and subsequent oxidation of the organoborane was chromatographed on alumina (70 g.). Elution with pentane gave starting material (500 mg.), while elution with pentane–benzene (3:1) gave 5α-cholestan-7β-ol (290 mg., 0.75 mmole, 38%), m.p. 113–114° (from methanol–ether), $[\alpha]_D$ +50°, lit.[10] m.p. 112–113°, $[\alpha]_D$ +52°. Oxidation with 8 *N* chromic acid in acetone at 0° gave 5α-cholestan-7-one, m.p. 116–117° (from methanol), $[\alpha]_D$ −45°, lit.[10] m.p. 116–118°, $[\alpha]_D$ −42°.

Elution then with pentane–benzene (1:1) gave 5α-cholestan-6α-ol (120 mg., 0.31 mmole, 16%), m.p. 126–128° (from ether–methanol), $[\alpha]_D$ +36°, lit.[4] m.p. 128–129°, $[\alpha]_D$ +35°. Oxidation with 8 *N* chromic acid in acetone at 0° gave 5α-cholestan-6-one, m.p. 95–97° (from methanol), $[\alpha]_D$ +7°, lit.[11] m.p. 96–98°, $[\alpha]_D$ +5°.

Acknowledgment.—The author would like to thank Dr. M. Green of this university for useful discussions.

(9) L. Ruzicka, H. Brüngger, E. Eichenberger, and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).
(10) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).
(11) C. W. Shoppee and G. H. R. Summers, *ibid.*, 3361 (1952).

Buxus Alkaloids. IX.[1] The Isolation and Constitution of Cyclobuxoxine[2]

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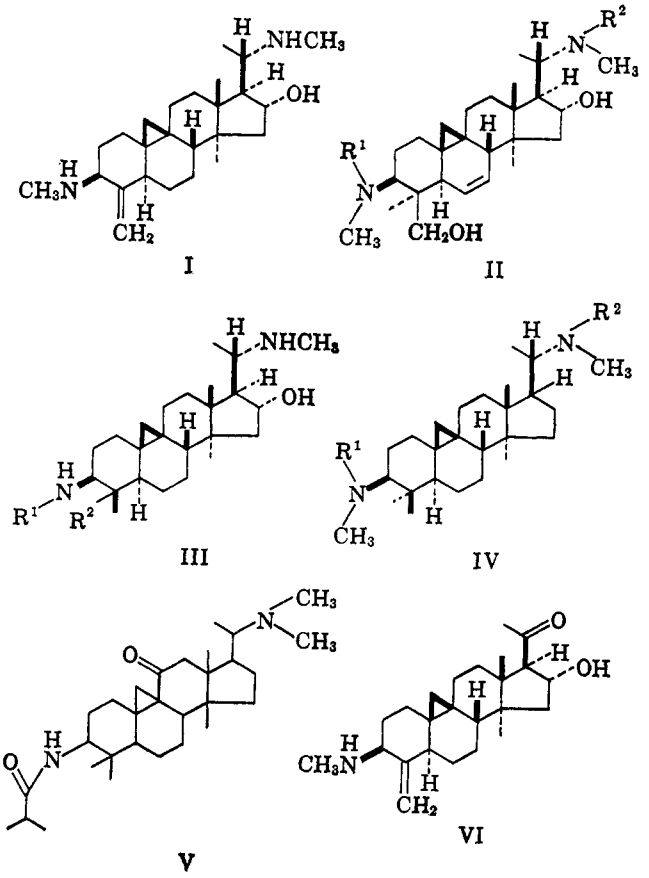
Received June 1, 1965

In 1962, we reported the elucidation of structure[3] and configuration[4] of cyclobuxine-D (I), an alkaloid isolated from *Buxus sempervirens* L.[5] Cyclobuxine-D was shown to be the prototype of a new class of steroidal alkaloids which contain a cyclopropane ring and which have a substitution pattern at C-4 and C-14 which is intermediate in the biogenetic scheme, between lanosterol- and cholesterol-type steroids. Subsequent studies have characterized the following structurally related alkaloids (see Chart I): cyclomicrophylline-A

CHART I



(II, $R^1 = R^2 = CH_3$),[6] cyclomicrophylline B (II, $R^1 = CH_3$; R^2 = H),[6,7] cyclomicrophylline-C (II, R^1 = H; $R^2 = CH_3$),[6] cyclobuxamine-H (III, $R^1 = R^2$ = H),[8] cyclovirobuxine-D (III, $R^1 = R^2 = CH_3$),[9] cycloprotobuxine-C (IV, R^1 = H; $R^2 = CH_3$),[10] cycloprotobuxine-D (IV, $R^1 = R^2$ = H),[1] and baleabuxine (V).[7] In addition, several new alkaloids containing a novel 9(10→19)-*abeo*-steroidal diene system have recently been isolated from *Buxus sempervirens* L.[11,12] The isolation from *Buxus sempervirens* L. and elucidation of the structure of an additional new alkaloid, cyclobuxoxine (VI), are described in the present report.

Cyclobuxoxine was isolated from the "weak bases" fraction obtained by the fractionation procedure described earlier.[3b] Adsorption chromatography on basic Woelm grade III alumina yielded cyclobuxoxine, $C_{24}H_{37}NO_2$, m.p. 181–183°, $[\alpha]^{27}_D$ +169° (*c* 0.63, chloroform). The n.m.r. data for cyclobuxoxine and its derivatives are shown in Table I. Its infrared spectrum, in Nujol, showed bands attributable to hydroxy and amino functions (2.82 and 2.97 μ), a carbonyl group (5.91 μ), and a terminal methylene group (6.18 and 11.18 μ).

(1) Part VIII: S. M. Kupchan and E. Kurosawa, *J. Org. Chem.*, **30**, 2046 (1965).
(2) This investigation was supported in part by Public Health Service Research Grants HE-02275 and HE-02952, from the National Heart Institute.
(3) (a) K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590 (1962); (b) *ibid.*, **86**, 4414 (1964).
(4) K. S. Brown, Jr., and S. M. Kupchan, *ibid.*, **84**, 4592 (1962); **86**, 4424 (1964).
(5) K. Heusler and E. Schlittler, *Helv. Chim. Acta*, **32**, 2226 (1949).
(6) T. Nakano and S. Terao, *Tetrahedron Letters*, 1035, 1045 (1964).
(7) D. Gaulier, F. Khuong-Huu-Lainé, E. Stanislas, and R. Goutarel, *Bull. soc. chim. France*, 657 (1965).
(8) K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **86**, 4430 (1964).
(9) K. S. Brown, Jr., and S. M. Kupchan, *Tetrahedron Letters*, 2895 (1964). The convention on use of letter suffixes to designate substitution pattern at C-3 and C-20 nitrogen functions is described in this paper.
(10) J. P. Calame and D. Arigoni, *Chimia* (Aarau), **18**, 185 (1964).
(11) S. M. Kupchan and W. L. Asbun, *Tetrahedron Letters*, 3145 (1964).
(12) D. Stauffacher, *Helv. Chim. Acta*, **47**, 968 (1964).