Bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) Disulfide.—3-*S*-Acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose[12] (0.25 g) was deacetylated and oxidized as above to give crystalline bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) disulfide (0.13 g, 60%). Two recrystallizations from hexane gave pure material with mp 108–109°; $[\alpha]^{25}D$ +64° (*c* 0.9, $CHCl_3$); uv max 249 mμ (ε 280); nmr ($CDCl_3$) τ 4.20 (d, 1, $J_{1,2}$ = 3.5 Hz, H_1), 5.20 (t, 1, $J_{2,3}$ = 4.5 Hz, H_2), 5.57–6.10 (m, 4, H_4, H_5, $H_{6,6'}$), 6.65 (doublet of doublets, 1, $J_{3,4}$ = 10 Hz, H_3), 8.45, 8.52, 8.62, 8.64 (3 H singlets, $2CMe_2$).

Anal. Calcd for $C_{24}H_{38}O_{10}S_2$: C, 52.35; H, 6.96; S, 11.64. Found: C, 52.48; H, 7.21; S, 11.47.

Registry No.—**2**, 24679-85-4; **3**, 24679-84-3; **4**, 24679-86-5; **5**, 24679-87-6; **6**, 31735-45-2; **8**, 25050-39-9; **10**, 31735-46-3; **12**, 31729-55-2; **13**, 31729-56-3; **15**, 31729-57-4; 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose, 28251-80-1; bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose-3-yl) disulfide, 31790-92-8.

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Structure of Anhydro Butenandt Acid

DAVID L. DREYER

Department of Chemistry, San Francisco State College,[1] San Francisco, California 94132, and Fruit and Vegetable Chemistry Laboratory,[2] Pasadena, California 91106

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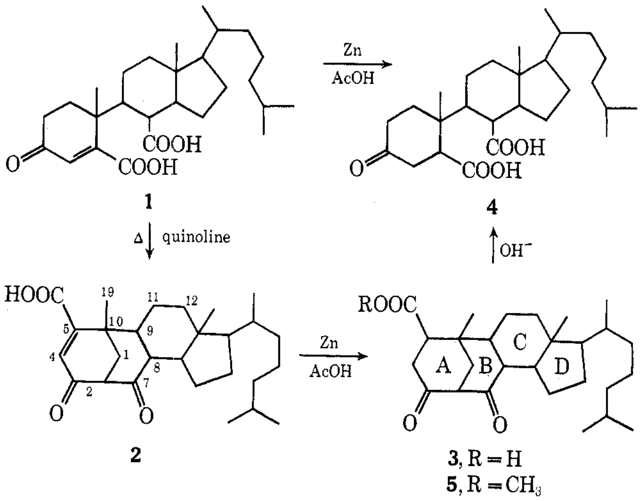
Chemical and spectroscopic evidence has confirmed the structure of anhydro Butenandt acid (**2**), for which an improved preparation is described. The saturated nonenolizable β-diketone **3** obtained from **2** had relatively high intensity ultraviolet absorption indicating the presence of a homoconjugated system. CD measurements on **3** and its methyl ester suggest that it exists as an equilibrium mixture of the boat–chair and twin-chair conformers at room temperature.

In 1953, Fieser,[3] in studies of the oxidation products of cholesterol, reported the preparation of a novel conversion product of Butenandt acid (**1**) for which structure **2** was suggested.



1

4

2

3, R = H
5, R = CH_3

Anhydro Butenandt acid (**2**) was obtained by heating **1** with quinoline or with acetic anhydride and boron trifluoride etherate. The original evidence for structure **2** consisted of (a) the similarity of the ultraviolet spectrum to that of other enedione systems,[3,4] (b) the infrared spectrum, which showed bands assigned to an acid and six-ring ketone, an α,β-unsaturated ketone, and a double bond, and (c) mild base hydrolysis, which gave back **1**, suggesting a β-diketone system.

The nmr spectrum of the anhydro acid **2** supports the suggested structure in complete detail. The nmr spectrum had an ill-resolved triplet centered at δ 3.56 (J = 2 Hz), which was assigned to the bridgehead proton between the two carbonyl groups.[5] The low value of the coupling constant is due to the fixed orientation of the bridgehead proton with respect to the neighboring methylene bridge with an angle such that the coupling constant is near a minimum.[6] The vinyl proton gave rise to a doublet at δ 7.05 (J = 1 Hz). The splitting of this band appears due to long-range coupling with the bridgehead proton.[7] Such coupling across four single bonds appears to be at a maximum when the interacting protons are confined to a planar zigzag configuration. The C-19 methyl resonance occurred at δ 1.57.

Preparation of compound **2** could be improved by exhaustive oxidation of cholesterol,[3,8] isolation of the total acid fraction, and heating this with quinoline without purification. The yield of **2** from cholesterol was thus about 15% in a much shorter working time. Repeated attempts to prepare a 2,4-dinitrophenylhydrazone or semicarbazone of **2** were unsuccessful. However, a high-melting bisoxime could be formed.

Attempted addition of bromine to **2** in glacial acetic acid or chloroform resulted in recovery of starting material. The anhydro acid **2** rapidly took up 1 mol of hydrogen over Pd/C to give **3**. The anhydro acid **2** could also be reduced to **3** by refluxing with excess zinc dust in glacial acetic acid. This latter reaction provides chemical evidence for the presence of an enedione system in **2**. Attempted reduction of the enedione system

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[1] Correspondence should be directed to this address.

[2] A laboratory of the Western Utilization Research and Development Division, U. S. Department of Agriculture.

[3] L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4386 (1953).

[4] P. Yates and G. F. Fields, *ibid.*, **82**, 5764 (1960).

[5] Similar values can be found for a bridgehead proton between two carbonyl groups in "citrylidenemalonic acid:" C. E. Berkoff and L. Crombie, *J. Chem. Soc.*, 3734 (1960); see also W. Herz and G. Caple, *J. Amer. Chem. Soc.*, **84**, 3517 (1962).

[6] *Cf.* L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 280.

[7] Reference 6, p 334. For similar cases of long-range coupling, see C. Lehmann, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 1031 (1962); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 121; N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Amer. Chem. Soc.*, **87**, 302 (1965).

[8] L. F. Fieser, W. Huang, and T. Goto, *ibid.*, **82**, 1688 (1960).

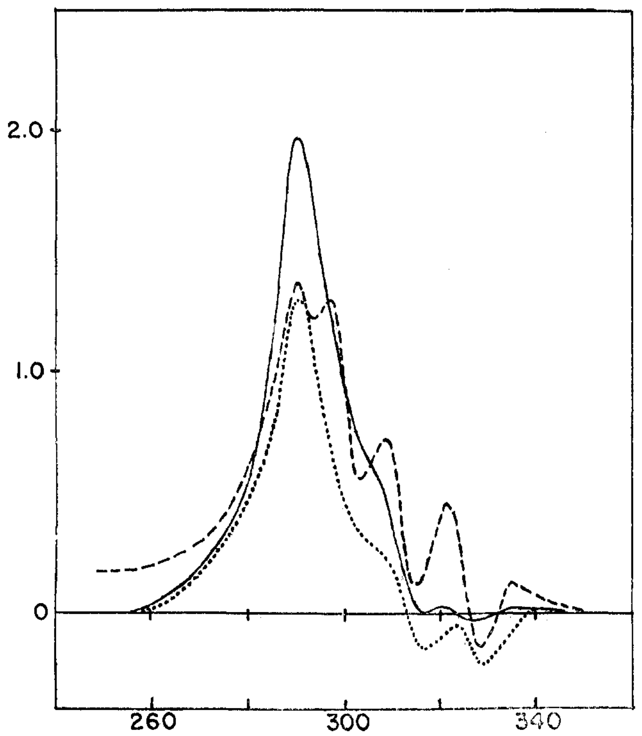


Figure 1.—CD spectrum of **3** at 25°, ····; CD spectrum of **3** at −67°, ----; CD spectrum of **5** at 25°, ——.

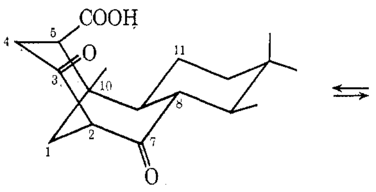
with tin and hydrochloric acid[9] was unsatisfactory possibly because of concurrent hydrolysis of the β-diketone system to dihydro Butenandt acid.

Since the catalytic addition of hydrogen to the double bond of **2** must occur on the least hindered face, the acid group in **3** must be in the β position.

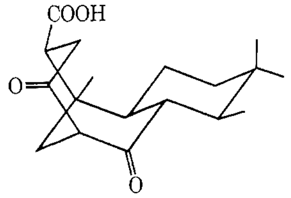
The nmr spectrum of **3** showed the same triplet due to the bridgehead proton at δ 3.60 (J = 3.3 Hz) and a band at δ 1.54 due to the C-19 methyl group.[10] Saponification of **3** with 5% aqueous sodium hydroxide gave dihydro Butenandt acid (**4**). This reaction provides additional chemical evidence for the presence of a β-diketone system in **2** and **3**. The formation of **2** from **1** can be regarded as a further example of an intramolecular Claisen acylation, a reaction which appears to be of some generality for the formation of bridged systems.[11]

The conformation of the A ring in the β-diketone **3** remains to be considered. The dihydro derivative **3** can exist in two possible forms in which the A ring can assume either a boat or a chair conformation.[12] Models indicate that the boat-chair conformation **3a** suffers from 1,4-flagpole interactions as well as badly forcing the carboxyl group into both H-8 and the 11β-hydrogen. In the twin-chair conformation **3b**, the 4β hydrogen is closer to H-8 than in normal boat flagpole interactions, but the carboxyl group is considerably less crowded and is close only to the 1β hydrogen.

The CD curve of the dihydro derivative **3** was temperature dependent, indicating that it was a mixture of the two possible conformers at room temperature. The CD curve showed both positive and negative components and resembled that of other conformationally mobile, temperature-dependent systems.[13]



3a, boat-chair



3b, twin-chair

The CD curves of the dihydro compound **3** measured at 25 and −67° are displayed in Figure 1. These curves may be interpreted as a relatively unstructured broad positive band centered at 300–305 mμ, partly superimposed on a weak negative Cotton effect curve at slightly longer wavelengths which possesses extensive fine structure. Since the extrema of both components of the curve lie well above the 280–285-mμ region associated with the n → π* transition of an isolated carbonyl group, the β-dicarbonyl system as a whole is acting as a single chromophore. The relatively high intensity and position at longer wavelengths of the uv maxima of **3** compared to saturated ketones supports the homoconjugated nature of the chromophore (Table I). Since the positive CD curve is enhanced at the expense of the negative curve with decreasing temperature, one may reasonably postulate an equilibrium between the two conformations (**3a** and **3b**) of the bicyclononadione system. It remains to predict that the sign of the Cotton effect in one of these two conformations and to show that the temperature effect is not due to solvation.

TABLE I

ULTRAVIOLET MAXIMA OF **3** IN DIFFERENT SOLVENTS

Solvent	λ_{max} (ε), mμ				
Methanol	~284		309 (180)		
Acetonitrile	~284	~298	~310	316 (180)	
Methylene chloride	~284	~300	~310	316 (165)	
Dioxane	~284	~302	~311	318 (170)	
Benzene		~300	~312	319 (185)	~328
Cyclohexane[a]	~286	~302	312	321	~330

[a] The low solubility of **3** in cyclohexane makes accurate measurements of the intensities uncertain.

Models indicate that the acid group in the twin-chair conformation **3b** is severely crowded by the axial protons at C-8 and C-11. If this were so, then increasing

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(9) J. P. Schaefer, *J. Org. Chem.*, **25**, 2027 (1960).

(10) The keto bands in the infrared of both bicyclic derivatives, **2** and **3**, were shifted toward lower energies by about 35 cm^{-1} from the accepted values. W. J. Wechter and G. Slomp, *J. Org. Chem.*, **27**, 2549 (1962), have remarked on the abnormally low carbonyl frequency of some bicyclic ketones. See also W. Thielacker and W. Schmid, *Justus Liebigs Ann. Chem.*, **570**, 15 (1950); W. Thielacker and E. Wegner, *ibid.*, **664**, 125 (1963); D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **76**, 2753 (1964).

(11) See, for example, G. Komppa and S. Beckmann, *Ber.*, **69**, 2783 (1936); O. Aschan, *Justus Liebigs Ann. Chem.*, **410**, 240 (1915); W. Herz, *J. Amer. Chem. Soc.*, **79**, 5011 (1957); Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos, and C. Podesva, *Tetrahedron*, **18**, 1433 (1962); K. Wiesner, F. Bickelhaupt, D. R. Babin, and M. Goetz, *ibid.*, **9**, 254 (1960); B. E. Hudson, C. R. Hauser, R. F. B. Cox, and S. M. McElvain, *J. Amer. Chem. Soc.*, **56**, 2459 (1934); R, Fusco and F. Tenconi, *Tetrahedron Lett.*, 1313 (1965).

(12) For a summary of current knowledge on the conformation of bicyclo-[3.3.1]nonanes, see M. Fisch, S. Smallcombe, J. C. Germain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970), and references cited therein.

(13) See, for example, C. Djerassi, *Proc. Chem. Soc.*, 314 (1964).

the bulk on the acid group should increase the relative amount of the boat–chair form **3a** at the expense of the twin-chair form **3b**. The contribution of the twin-chair form **3b** to the CD curve should decrease while the intensity of those peaks due to the boat–chair form **3a** should increase. A simple derivative of **3** with increasing bulk on the acid group is its methyl ester **5**. The CD curve of the methyl ester **5** (Figure 1) showed much less contribution by the negative components of the curve. Thus, the broad positive CD band is due to the boat–chair form **3a** and a negative band at longer wavelengths showing fine structure is due to the twin-chair conformation **3b**.

The more symmetrical twin-chair conformation **3b** has a better geometry for overlap between the two keto carbonyl groups. Therefore, the Cotton effect in this conformer is at higher wavelength and has more fine structure, a feature generally associated with homoconjugated systems.

Prediction of the sign of the Cotton effect for **3a** and **3b** from octant rules is not straightforward since vicinal effects of diketones cannot always be predicted and their magnitude appears to depend upon distance and relative positions of the two carbonyl groups.[14]

Experimental Section[15]

Anhydro Butenandt Acid. Δ^4-7(6→2)*abeo*-cholestane-3,7-dion-6-oic Acid (**2**).[2,8]—A solution of 150 g of sodium dichromate in 400 ml of glacial acetic acid at 10° was added to a solution containing 40 g of cholesterol in 400 ml of glacial acetic acid at 20°. The resulting mixture was kept at 15° for 1 hr and then left overnight at room temperature. A large volume of water was then added and the solution extracted with 5% bicarbonate solution. Further work-up of the neutral fraction gave small amounts of Δ^4-cholestene-3,6-dione and cholestane-3,6-dion-5α-ol.[1] The bicarbonate extracts were backwashed with ether and acidified, and the acid fraction was collected by extracting with ether. The ether was removed to give an off-color glass, to which 15 ml of quinoline was added. The mixture was heated at 180° for 20 min and then at 210–220° for 15 min. This reaction mixture was allowed to cool and then taken up in ether. The ether solution was washed with dilute hydrochloric acid and water. The ether phase was extracted with 20-ml portions of 5% sodium bicarbonate. Each portion was acidified separately with hydrochloric acid. The last portion was occasionally somewhat oily and, if so, was best worked up separately. The acid was collected, washed with water, and dried. The product was crystallized from benzene–petroleum ether (bp 30–60°) or dichloroethane–petroleum ether several times for analysis: mp 223.5–226°; $\lambda_{\max}$ (ethanol) 213 (5300), 239 mμ (7000); $\lambda_{\max}$ (cyclohexane) 236, ~300 mμ; ir (Nujol) ν 1728 (acid and six-ring ketone), 1642 (α,β-unsaturated ketone), 1595 cm^{-1} (double bond); yield 6–8 g (the acid took up 1.1 mol of hydrogen over Pd/C in ethanol); ORD in methanol (*c* 0.009, 30°) $[\alpha]_{400}$ −200°, $[\alpha]_{323}$ +5900°, $[\alpha]_{286}$ −9100°, $[\alpha]_{250}$ +3600°, $[\alpha]_{214}$ −13,100°, $[\alpha]_{210}$ −9200° (last reading) (the profiles of the ORD curves in dioxane and cyclohexane were almost identical with those in methanol); CD (*c* 0.0016, dioxane, 30°) 430 (0), 388 infl (−1.38), 320 (−1.88), 305 (+11.1), 269 (−6.75), 262 (−5.87) (last reading).

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.6; H, 9.27.

Dihydro Derivative. 7(6→2)*abeo*cholestane-3,7-dion-6-oic Acid (**3**).—The anhydro Butenandt acid was refluxed with excess zinc dust in glacial acetic acid for 1.5 hr, cooled, and filtered from the excess zinc dust, and water was added to the cloud point. The dihydro acid **3** separated and was recrystallized several times from acetic acid–water for analysis: mp 202–206°; ir (Nujol) ν 1726 (acid), 1675 cm^{-1} (ketone) (when the reaction was run for 12–24 hr, no product could be isolated in a pure condition); ORD in dioxane (*c* 0.001, 30°) $[\alpha]_{350}$ −1800°, $[\alpha]_{323.5}$ −4720°, $[\alpha]_{324}$ −860°, $[\alpha]_{319}$ −1720°, $[\alpha]_{312}$ +2660°, $[\alpha]_{307.5}$ +2000°, $[\alpha]_{302}$ +4200°, $[\alpha]_{280-270}$ −7720° (broad trough), $[\alpha]_{263}$ −7370°, $[\alpha]_{232}$ −15,500°, $[\alpha]_{225}$ −11,800° (last reading); CD (*c* 0.003, ethanol, 25°) 352 (0), 340 (0.06), 329 (−0.21), 323 (−0.06), 317 (−0.13), 307 infl (0.29), 291 (1.27), 256 (0) (last reading); CD (*c* 0.008, ethanol, −67°) 358 (0), 335 (0.14), 328 (−0.14), 321 (0.46), 315 (0.12) 308 (0.71), 303 (0.56), 297 (1.30), 294 (1.21), 290 (1.38), 256 (0.19), 248 (0.19) (last reading); CD (*c* 0.008, dioxane, 30°) 350 (0), 340 (0.05), 328 (−0.58), 321 (−0.29), 315 (−0.58), 307 (−0.07), 304 (−0.10), 294i (0.80), 290 (0.89), 260 (0), 252–264 (−0.07), 248 (−0.32) (last reading).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.3; H, 9.83. Found: C, 75.2; H, 9.84.

Saponification of 3.—The dihydro derivative **3** was dissolved in 5% sodium hydroxide and refluxed for 1.5 hr. The solution was allowed to cool whereupon the sodium salt of **4** crystallized in needles. This was collected, dissolved in methanol, and acidified with hydrochloric acid, and the product was collected with ether, washed, and dried. The product crystallized upon concentration of the ether and addition of petroleum ether, mp 208–209.5°. Mixture melting point with a sample of **4**, prepared according to the method of Fieser,[3] showed no depression. The infrared spectra of the two samples were also identical: ir (Nujol) ν 1736 (acid), 1658 cm^{-1} (ketone).

Bisoxime of Anhydro Butenandt Acid.—Equal weights of **2** and hydroxylamine hydrochloride were refluxed in a 1:1 mixture of anhydrous pyridine and absolute ethanol for 4 hr. The solution was concentrated, water was added, and the solution was then extracted with ether. The ether phase was washed and dried and, upon concentration, the product separated, mp 268–269° dec from ethanol–water. The infrared spectrum showed unresolved hydroxy absorption: (Nujol) ν 1693 (acid), 1640, 1615, 1587 cm^{-1} (C=C and C=N); $\lambda_{\max}$ 265 mμ (ethanol–sodium hydroxide). The oxime was very soluble in ethanol and insoluble in acetic acid.

Anal. Calcd for $C_{27}H_{42}O_4N_2$: C, 70.70; H, 9.23. Found: C, 70.3; H, 9.12.

Methyl Ester of 3 (**5**).—Compound **3** was treated with excess diazomethane. The ether solvent was removed and the residue filtered through a short column of alumina with benzene. Removal of the benzene gave a gum which appeared homogeneous on tlc but could not be induced to crystallize under a variety of conditions: nmr δ 3.75 (methoxy), 3.25 (H-2), 1.30, 0.92, 0.92, 0.83, 0.67 (*C*-methyls); CD (*c* 0.0007, ethanol, 30°) 350 (0), 335 (0.01) 327 (−0.008), 320 (0.01), 317 (0.008), 306 infl (0.62), 290 (1.98), 255 (0.).

Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.66; H, 9.94. Found: C, 75.8; H, 9.93.

Registry No.—**2,** 32174-69-9; **2** bisoxime, 32256-04-5; **3a,** 32174-70-2; **3b,** 32174-71-3; **5,** 32174-72-4.

Acknowledgment.—The author is grateful to Mr. L. M. White for the analytical data, to Mr. J. Stewart for the ORD and CD curves, and to Dr. W. E. Thiessen for helpful discussions.

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(14) G. Snatzke and G. Eckhardt, *Tetrahedron*, **24**, 4543 (1968); G. Snatzke and H. W. Fehlhaber, *ibid.*, **20**, 1243 (1964).

(15) For CD notation see, G. Snatzke, *Tetrahedron*, **21**, 421 (1965). Nmr spectra were obtained at 60 MHz in deuteriochloroform and are given in δ relative to internal TMS. The relative areas of the peaks were consistent with the assignments.