The Synthesis of *d*- and *l*-Sirenin and Their Absolute Configurations

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Abstract: The synthesis of *d*- and *l*-sirenin is described. Optical resolution was accomplished by a gas–liquid chromatographic separation of the diastereomeric ketals of the bicyclic ketone **2**, formed from optically active 2,3-butanediol, a short synthesis of which is presented starting from tartaric acid. The absolute configuration of natural *l*-sirenin (**1**) is assigned by conversion of monodeoxysirenin (**14**) into the parent hydrocarbon, sesquicarene **(15)**, and by the circular dichroism absorptions of the saturated bicyclic ketones **22** and **23**.

In previous publications,[2] the powerful sperm attractant sirenin was shown to have structure **1**. Subsequent syntheses of sirenin as its racemate[3] confirmed the structural assignment. Sirenin was postulated to have the absolute configuration[2c] as indicated in **1**, although this assignment was not rigorously established. In order to settle conclusively the question of absolute stereochemistry as well as continue our program of biological evaluation of sirenin, we undertook the synthesis of *d*- and *l*-sirenin. The results of this study are now reported.

Resolution. Our previously reported synthetic scheme for *dl*-sirenin[3a,d] allowed a flexible choice of intermediates for effecting optical resolution. However, from the onset it was decided to effect a resolution by means of a gas chromatographic separation of diastereomers,[4] since with this method both enantiomers can be obtained and in addition, no independent procedure for establishing optical purity is required. Accordingly, we examined the glpc separation of diastereomeric ketals[4a] of bicyclic ketone **2** and diastereomeric *sec*-butyl esters[4b-f] of acid **13** (R = CO_2H, unresolved).

In the case of *sec*-butyl ester **13** (R = *sec*-butyl)[5] only partial or no separation of diastereomers was observed on a wide range of liquid phases. For bicyclic ketone **2** on the other hand, the diastereomeric ketals formed by reaction of **2** with optically active 2,3-butanediol were cleanly separated on an SE-30 column, which was the only liquid phase of many tried that gave a good separation. Consequently, the optical resolution was performed on bicyclic ketone **2**. Resolution at this stage was advantageous in that **2** represents the compound where asymmetry is first introduced into the molecule and moreover, this would permit the application of circular dichroism to determination of absolute configuration in view of the extensive literature[6] on ORD and CD of conjugated cyclopropyl ketones.

When this work was first started there was no available commercial source of resolved 2,3-butanediol.[7] Although its optical resolution has been reported,[8] the recovery of glycol is very low. A synthesis of both enantiomorphic 2,3-butanediols starting from the D- and L-mannitols has been carried out[9] as the final proof of absolute configuration of the diols; however, this sequence does not lend itself to preparative scale. As a result, the preparation of L(+)-2,3-butanediol from readily available L(+)-tartaric acid was undertaken. Our synthesis was based upon the hydrogenolysis of dimesylate **8** which was prepared by a published sequence of reactions.[10] Thus natural tartaric acid was esterified[11] to ethyl ester **5** which was converted[10] to the acetonide **6** by an acid-catalyzed reaction with acetone in petroleum ether under simultaneous azeotropic removal of the water. Reduction[10] of the ester groups with lithium aluminum hydride in ether gave the threitol **7** from which **8** was obtained by reaction with methanesulfonyl chloride in pyridine at −5°. Hydrogenolysis of the mesyl groups was effected by interaction of **8** with lithium aluminum hydride in tetrahydrofuran to give acetonide **9** in 78% yield. The physical properties of **9** were identical with those reported[9] for its preparation from the ditosylate of **7** in lower yield by the Freudenberg–Raschig deoxygenation procedure. The final transformation of deketalization was effected in 91% yield by hydrolysis with dilute hydrochloric acid to give L(+)-2,3-butanediol (**10**).

Reaction of bicyclic ketone **2** with both D(−)-2,3-butanediol[7] and L(+)-2,3-butanediol in the presence

(1) National Institutes of Health Predoctoral Fellow.

(2) (a) L. Machlis, W. H. Nutting, M. W. Williams, and H. Rapoport, *Biochemistry*, **5**, 2147 (1966); (b) L. Machlis, W. H. Nutting, and H. Rapoport, *J. Amer. Chem. Soc.*, **90**, 1674 (1968); (c) W. H. Nutting, H. Rapoport, and L. Machlis, *ibid.*, **90**, 6434 (1968).

(3) (a) J. J. Plattner, U. T. Bhalerao, and H. Rapoport, *ibid.*, **91**, 4933 (1969); (b) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *ibid.*, **91**, 4318 (1969); (c) P. A. Grieco, *ibid.*, **91**, 5660 (1969); (d) U. T. Bhalerao, J. J. Plattner, and H. Rapoport, *ibid.*, **92**, 3429 (1970); (e) E. J. Corey and K. Achiwa, *Tetrahedron Lett.*, 2245 (1970).

(4) (a) J. Casanova, Jr., and E. J. Corey, *Chem. Ind. (London)*, 1664 (1961); (b) H. C. Rose, R. L. Stern, and B. L. Karger, *Anal. Chem.*, **38**, 469 (1966); (c) E. Gil-Av, R. Charles-Sigler, G. Fischer, and D. Nurok, *J. Gas Chromat.*, **4**, 51 (1966); (d) G. E. Pollock and D. A. Jermany, *ibid.*, **6**, 412 (1968); (e) G. E. Pollock, V. I. Oyama, and R. D. Johnson, *ibid.*, **3**, 174 (1965); (f) G. E. Pollock and V. I. Oyama, *ibid.*, **4**, 126 (1966).

(5) Prepared by transesterification of the known[3a,d] methyl ester.

(6) (a) K. Kuriyama, H. Tada, Y. K. Sawa, S. Ito, and I. Itoh, *Tetrahedron Lett.*, 2539 (1968); (b) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965); (c) W. Reusch and P. Mattison, *ibid.*, **24**, 4933 (1968); (d) K. Schaffner and G. Snatzke, *Helv. Chim. Acta*, **48**, 347 (1965).

(7) An initial small sample of D-(−)-2,3-butanediol was provided by Dr. G. Helmkamp, University of California, Riverside, to whom we are grateful. Subsequently we learned this material is available from Burdick and Jackson, Muskegon, Mich. ($1.50 per gram).

(8) (a) K. A. Thaker and N. S. Dave, *J. Sci. Ind. Res.*, **20B**, 329 (1961); (b) J. Boeseken and R. Cohen, *Recl. Trav. Chim. Pays-Bas*, **47**, 839 (1928).

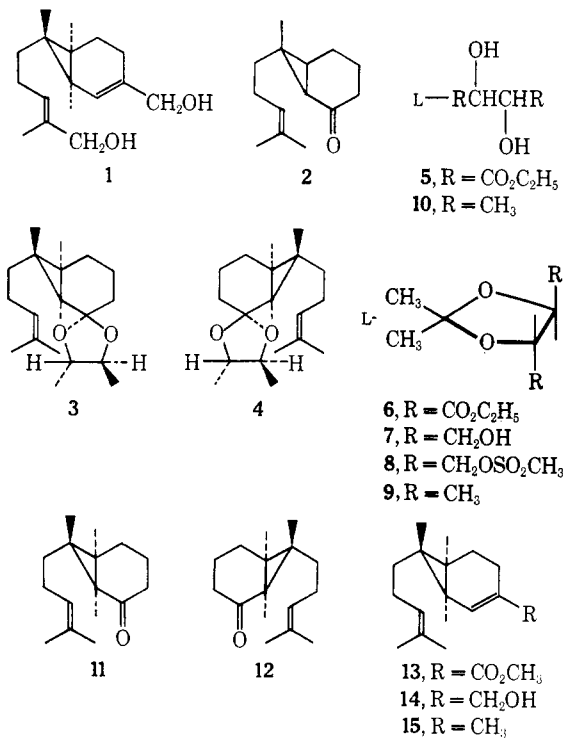
(9) L. J. Rubin, H. A. Lardy, and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **74**, 425 (1952).

(10) P. W. Feit, *J. Med. Chem.*, **7**, 14 (1964).

(11) T. M. Lowry and J. O. Cutter, *J. Chem. Soc.*, **121**, 532 (1922).

of *p*-toluenesulfonic acid was carried out and in each case gave a diastereomeric mixture of ketals in 95% yield. Preparative glpc of the D-diol ketals afforded the pure diastereomers **3** and **4**,[12] whereas glpc separation of the L-diol ketals gave the respective enantiomers, **3′** and **4′**. Ketals **3** and **4** were separately hydrolyzed with aqueous phosphoric acid in ethanol at 25° to give bicyclic ketones **11** and **12**, respectively, after chromatographic purification over silica gel. Similar hydrolysis of the L-diol ketals **3′** and **4′** followed by chromatographic purification gave **12** and **11**, respectively. Both ketones were homogeneous according to glpc analysis and had equal and opposite specific rotations. From this point the syntheses were carried out using essentially the same experimental conditions as previously described[3d] to give both *d*- and *l*-sirenin.[13] Interestingly, (+)-ketone **11** was transformed into (+)-unsaturated ester **13** which gave (−)-sirenin and (−)-monodeoxysirenin (**14**). Analogous sign reversal of specific rotation was observed with the (−)-unsaturated ester in going to (+)-monodeoxysirenin and (+)-sirenin.

Absolute Configuration. Previously[2c] the absolute configuration of sirenin was postulated to be the same as that of its parent hydrocarbon, sesquicarene (**15**),



since both compounds have the same sign of specific rotation. This assumption requires that the introduction of the two oxygen atoms into **15** has no effect upon the sign of its specific rotation. A more rigorous correlation is required and we have therefore applied circular dichromism studies as well as direct chemical correlation to this problem.

(12) Structures **3** and **4** denote absolute configurations since the absolute configuration of D-(−)-2,3-butanediol has been established [S. A. Morell and A. H. Auernheimer, *J. Amer. Chem. Soc.*, **66**, 792 (1944)] and that of the ketones assigned in the present work.

(13) The biological activity of the separate isomers, along with that of sirenin analogs, will be discussed in a future publication on structure–activity relationships.

Sesquicarene has been assigned the stereochemistry as indicated in **15** on the basis of the following considerations.[14] Since **15** and its tetrahydro derivative **16** show closely related but opposite specific rotations, −76.9 and +19.8°, respectively, to those of (+)-2-carene (**17**), +76.36°, and (−)-*cis*-carane (**18**), −17.8°, **15** was postulated to have the same absolute configuration as (−)-2-carene. This postulate was corroborated by the CD absorption of ketone **19** (derived from sesquicarene) which showed positive Cotton effects at 287 and 217 nm. The Cotton effect for the latter π–π^* transition is in complete agreement with the above correlation but the Cotton effect for the former n–π^* transition is not; however, recent publications have pointed out the possibility of anomalous Cotton effects[6a,b] in the n–π^* transitions for conjugated cyclopropyl ketones, while demonstrating the reliability of the Cotton effect in the π–π^* transition.

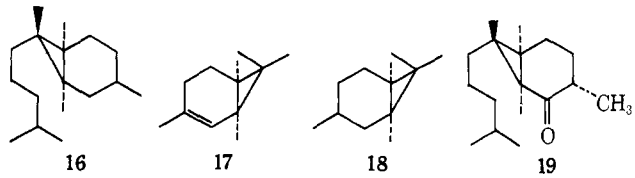
Since the absolute configuration of sesquicarene is known by the above evidence, the conversion of sirenin or one of its precursors into sesquicarene would allow a direct correlation of the two compounds. For this purpose (−)-monodeoxysirenin (**14**) was prepared from (+)-unsaturated ester **13** as previously described for the *dl* compounds.[3d] Attempted deoxygenation of **14** by sequential treatment with methanesulfonyl chloride–pyridine at −22° and lithium aluminum hydride at 0° gave a low yield of sesquicarene plus large amounts of rearranged olefins resulting from the cleavage of the cyclopropane ring.[15] Application of the procedure for allylic deoxygenation,[16] which involves reaction first with sulfur trioxide–pyridine complex followed by lithium aluminum hydride, afforded (−)-sesquicarene in 85% yield. Similar treatment of (+)-monodeoxysirenin gave (+)-sesquicarene. This result indicated that naturally occurring sirenin and sesquicarene have the same absolute configuration.

We next turned to an independent confirmation of the above result by means of circular dichroism studies. Since Cotton effects for the n–π^* transition for certain cyclopropyl ketones are known to be unreliable for predicting absolute configuration,[6a,b] it was necessary to prepare bicyclic ketones **22** and **23** from which the Cotton effect for the π–π^* transition could be obtained. Accordingly, ketals **3** and **4** were hydrogenated over 10% Pd–C to give ketals **20** and **21**, respectively, which were separately deketalized with aqueous phosphoric acid in ethanol. The resulting optically active ketones **22** and **23** were homogeneous according to glpc and had equal and opposite specific rotations. (+)-Ketone **22**, whose dehydro derivative (+)-**11** is the precursor to (−)-sirenin, showed positive Cotton effects at 287 and 214 nm. Analogous negative Cotton effects were observed for (−)-ketone **23**. As in the case with ketone **19** derived from sesquicarene, the Cotton effect for the π–π^* transition of ketone **22** predicts the correct absolute configuration, whereas Cotton effect for the n–π^* transition seems to be anomalous. Since ketones **19** and **22** differ only by the additional methyl group in **19** but have essentially identical Cotton effects for the n–π^* and π–π^* transitions, this would strongly indicate that the anomaly in

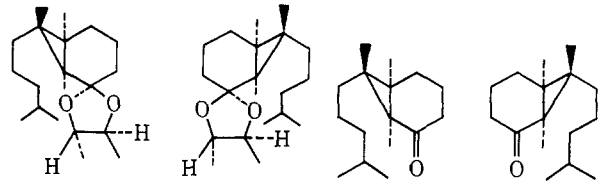
(14) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, 1251 (1968).
(15) E. J. Corey and K. Achiwa, *ibid.*, 1837 (1969).
(16) E. J. Corey and K. Achiwa, *J. Org. Chem.*, **34**, 3667 (1969).

the Cotton effect for the n–π^* transition results from the geminal alkyl substituents on the cyclopropane ring. Similar rationalization was postulated for the anomalous Cotton effect for the n–π^* transition in (+)-carone.[6b]

The combination of the above results, namely, direct conversion of (−)-monodeoxysirenin into (−)-sesquicarene and CD data on bicyclic ketones **22** and **23**, allows a conclusive assignment of sirenin's absolute stereochemistry as shown in **1**.



16 **17** **18** **19**



20 **21** **22** **23**

Experimental Section[17]

2,3-*O*-Isopropylidene-L-threitol 1,4-Dimethanesulfonate (8). A 195-g sample of diethyl L-tartrate[11] was converted[10] into 185 g (79%) of diethyl 2,3-*O*-isopropylidene-L-tartrate (**6**): bp 107–110° (1.4 mm); $[\alpha]^{23}D$ −51.2° (neat) [lit.[18] bp 150° (19 mm); $[\alpha]^{15}D$ −51.19° (neat)]; nmr 1.26 (6 H, t, J = 7 Hz, CH_2CH_3), 1.41 (6 H, s, *tert*-CH_3), 4.20 (4 H, q, J = 7 Hz, OCH_2CH_3), 4.60 (2 H, s, OCHCOOEt). Reduction of **6** (96 g) as described[10] gave 51 g (81%) of 2,3-*O*-isopropylidene-L-threitol **7**: bp 103–104° (0.2 mm); $[\alpha]^{22}D$ +4.1° (*c* 5, chloroform) [lit.[10] bp 96–96.5° (0.5 mm); $[\alpha]^{20}D$ +4.1 (*c* 5, chloroform)]; nmr ($CDCl_3$) 1.40 (6 H, s, *tert*-CH_3), 3.54–4.04 (8 H, m). Mesylation of **7** (49 g) by the published procedure[10] gave 72 g (75%) of **8**: mp 85–86°; $[\alpha]^{25}D$ −23.5° (*c* 2, acetone) [lit.[10] mp 85.5–86.5°; $[\alpha]^{20}D$ −21.3° (*c* 2, acetone)]; nmr ($CDCl_3$) 1.44 (6 H, s, *tert*-CH_3), 3.06 (6 H, s, $ROSO_2CH_3$), 4.01–4.55 (6 H, m).

2,3-*O*-Isopropylidene-L-butanediol (9). To a stirred solution of $LiAlH_4$ (17 g) in 200 ml of tetrahydrofuran was added dropwise over a period of 15 min the dimesylate (71 g) dissolved in 400 ml of tetrahydrofuran at 0–3°. Stirring for 24 hr at 25° was followed by stirring for 1 hr at reflux. After cooling in an ice bath, water (17 ml), 15% NaOH (17 ml), and water (34 ml) were sequentially added. The precipitate was removed and washed thoroughly with methylene chloride and ether. The combined organic extract was dried over magnesium sulfate and fractionally distilled through a 2-ft column packed with glass helices to give 22.6 g (78%) of acetonide **9**: bp 109–110°; $[\alpha]^{23}D$ +31.9° (*c* 1.34, chloroform) [lit.[9] bp 109.7°; $[\alpha]^{23}D$ +31.65° (*c* 4.96, chloroform)]; nmr 1.18 (6 H, d, J = 5.5 Hz, $OCHCH_3$), 1.31 (6 H, s, *tert*-CH_3), 3.48 (2 H, m, CHOR).

L(+)-2,3-Butanediol (10). The experiment was modeled after that reported for deketalization of the corresponding DL compound.[19] Ketal **9** (20 g) was mixed with 38 ml of 0.5 *N* HCl and heated at reflux with magnetic stirring while acetone was allowed to distil from a 1.5-ft column packed with glass helices. When the temperature reached 100°, the solution was cooled and neutralized to pH 7 with 5 *N* NaOH and then continuously extracted with ether. After evaporating the ether, the residue was fractionally distilled at reduced pressure. Redistillation gave 12.5 g (91%) of colorless diol: bp 86–87° (16 mm); $[\alpha]^{20}D$ +12.85° (neat) [lit.[9] $[\alpha]^{25}D$ +12.4° (neat)]. Since highly efficient columns are required to separate the last traces of water from butanediol these materials may contain a small amount of water.

Resolution of Bicyclic Ketones 11 and 12. A solution of 3.0 g (14.5 mmol) of ketone **2** and 2.6 g (29 mmol) of D(−)-2,3-butanediol in 50 ml of anhydrous benzene containing 10 mg of *p*-toluenesulfonic acid was heated for 2 hr with a Dean–Stark water separator. Ether was added and the mixture was extracted with aqueous sodium bicarbonate and water. After the ethereal extract was dried over sodium sulfate and the solvent evaporated, the residue was chromatographed over silica gel. Elution with benzene gave 3.9 g (96%) of the diastereomeric ketals. Preparative glpc (0.375 in. × 20 ft of 10% SE-30 on 60–80 mesh Chromosorb W, acid washed and DMCS treated, 212° column temperature) gave first ketal **3**: retention time 35.0 min; nmr 1.05 (3 H, singlet, *tert*-CH_3), 1.21 (6 H, d, J = 5.5 Hz, $OCHCH_3$), 1.60 (3 H, trans $C{=}CCH_3$), 1.65 (3 H, cis $C{=}CCH_3$), 3.52 (2 H, m, CHOR), 5.10 (1 H, t, J = 7 Hz, $C{=}CHCH_2$).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.7; H, 10.9. Found: C, 77.6; H, 10.7.

The next fraction was ketal **4**: retention time 37.5 min; nmr absorption same as for ketal **3**.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.7; H, 10.9. Found: C, 78.1; H, 11.1.

A mixture of 1.0 g of ketal **3** and 1 ml of 10% phosphoric acid in 10 ml of 95% ethanol was stirred at room temperature for 12 hr. The mixture was diluted with aqueous sodium bicarbonate solution and extracted with pentane. The pentane extract was chromatographed on silica gel to give 640 mg of ketone **11**: $[\alpha]^{24}D$ +157° (*c* 1.67, chloroform); CD $[\theta]_{287}$ +6110 (*c* 0.531 × 10^{-3} g/ml, methanol).

Similar hydrolysis of ketal **4** for 10 hr gave ketone **12**, $[\alpha]^{23}D$ −159° (*c* 1.34, chloroform); CD $[\theta]_{287}$ −6320 (*c* 0.248 × 10^{-3} g/ml, methanol).

Alternatively, reaction of ketone **2** with L(+)-2,3-butanediol was carried out as described for the D(−)-diol. Glpc separation then gave the separated ketals **3′** and **4′**, retention times 35.0 and 37.5 min, respectively. Hydrolysis of **3′** as above gave ketone **12**, $[\alpha]^{23}D$ −158° (*c* 0.56, chloroform). Similar treatment of **4′** gave ketone **11**, $[\alpha]^{23}D$ +157° (*c* 0.48, chloroform).

Resolution of Bicyclic Ketones 22 and 23. A solution of 967 mg of diastereomeric ketals **3** and **4** in 23 ml of absolute ethanol was shaken with 210 mg of 10% Pd/C and hydrogen at 25 psi for 7 hr. After removing the catalyst and evaporating the solvent, the residue was chromatographed on silica gel (elution with benzene) to give 740 mg of oil. Glpc separation (0.25 in. × 20 ft of 10% SE-30 on 60–80 mesh Chromosorb W, acid washed and DMCS treated, column temperature 212°) gave first ketal **20**: retention time 31.0 min; nmr 0.88 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 1.05 (3 H, s, *tert*-CH_3), 1.21 (6 H, d, J = 5.5 Hz, $OCHCH_3$), 3.52 (2 H, m, CHOR).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.1; H, 11.5. Found: C, 77.0; H, 11.7.

Next was obtained ketal **21**: retention time 33.5 min; nmr absorptions same as for ketal **20**.

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.1; H, 11.5. Found: C, 76.8; H, 11.6.

A mixture of 100 mg of ketal **20** and 0.15 ml of 10% phosphoric acid in 1.0 ml of absolute ethanol was kept at 25° for 10 hr. The mixture was diluted with aqueous sodium bicarbonate and extracted with pentane. The pentane extract was chromatographed on silica gel to give 54 mg of ketone **22**: retention time 22 min (10% SE-30 0.25 in. × 20 ft, 198°); $[\alpha]^{23}D$ +147° (*c* 0.61, $CHCl_3$) CD (1 mm cell): $[\theta]_{287}$ +9060, $[\theta]_{214}$ +11,020 (*c* 0.640 × 10^{-3} g/ml, methanol); nmr 0.88 (6 H, d, J = 7 Hz, $CH(CH_3)_2$), 1.09 (3 H, s, *tert*-CH_3), ir 1685 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.7; H, 11.6. Found: C, 80.6; H, 11.5.

Similar hydrolysis of ketal **21** gave ketone **23**: retention time 22 min (10% SE-30, 0.25 in. × 20 ft, 198°); $[\alpha]^{23}D$ −147° (*c* 0.57, $CHCl_3$); CD (1 mm cell) $[\theta]_{288}$ −8560, $[\theta]_{212}$ −11,440 (*c* 0.582 × 10^{-3} g/ml, methanol); nmr absorptions same for ketone **22**.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.7; H, 11.5. Found: C, 80.8; H, 11.6.

***d*- and *l*-Sirenin.** Syntheses were carried out using essentially the same experimental conditions as described earlier[3d] to give the following optically active intermediates (all compounds are liquids with rotations determined in chloroform): (+)-β-keto ester, $[\alpha]^{27}D$ +82.2° (*c* 1.67); (−)-β-keto ester, $[\alpha]^{28}D$ −85.7° (*c* 0.91); (+)-β-hydroxy ester, $[\alpha]^{23}D$ +27.1° (*c* 0.95); (−)-β-hydroxy ester, $[\alpha]^{26}D$ −22.5° (*c* 1.47); (+)-pivalate diester, $[\alpha]^{24}D$ +65.3° (*c* 1.57);

(17) All boiling and melting points are uncorrected. Microanalyses were performed by the Analytical Laboratory, University of California, Berkeley; nmr spectra are reported as δ values and were obtained in CCl_4 unless otherwise noted on a Varian T-60 spectrometer using internal TMS (δ = 0). Optical rotations were measured with a Zeiss or Bendix polarimeter. CD spectra were obtained on a Cary Model 60 spectropolarimeter.

(18) Y. Tsuzuki, *Bull Chem. Soc. Jap.*, **10**, 255 (1935).

(19) A. C. Neish, *Can. J. Res., Sect. B*, **25**, 423 (1947).

(−)-pivalate diester, $[\alpha]^{23}D$ −57.6° (*c* 1.73); (+)-unsaturated ester, $[\alpha]^{24}D$ +58.8° (*c* 1.61); (−)-unsaturated ester, $[\alpha]^{26}D$ −57.5° (*c* 1.47); (+)-monodeoxysirenin, $[\alpha]^{24}D$ +47.7° (*c* 3.00); (−)-monodeoxysirenin, $[\alpha]^{23}D$ −46.9° (*c* 2.74) [lit.[3d] $[\alpha]^{25}D$ −28° (*c* 1.0)]; (+)-sirenin, $[\alpha]^{25}D$ +42.9° (*c* 2.02); (−)-sirenin, $[\alpha]^{24}D$ −43.3° (*c* 1.42) [lit.[2a] −45° (*c* 1.0)].

Preparation of (+)- and (−)-Sesquicarene (15). The method was that of Corey and Achiwa.[15,16] To a solution of distilled (−)-monodeoxysirenin[3d] (124 mg, 0.563 mmol) in dry tetrahydrofuran (3 ml) was added at 0° pyridine–sulfur trioxide complex (218 mg, 1.37 mmol), and the mixture was stirred at 0–4° for 21 hr. A solution of 200 mg (5.28 mmol) of $LiAlH_4$ in 9 ml of tetrahydrofuran was added at 0° for 5 min and 25° for 5.5 hr. After careful addition of water (15 ml) the mixture was extracted with ether. The ethereal extract was dried over magnesium sulfate and the solvents were evaporated. Chromatography of the residue on silica gel (elution with hexane) gave 98 mg (85%) of (−)-sesquicarene: $[\alpha]^{24}D$ −75.4° (*c* 0.87, chloroform) [lit.[14] $[\alpha]^{25}D$ −76.9° (*c* 0.82, chloroform)]. The infrared and nmr data obtained were identical with those reported for natural sesquicarene. (+)-Sesquicarene was prepared in an analogous manner from (+)-monodeoxysirenin[3d] and had $[\alpha]^{26}D$ +75.8° (*c* 0.67, chloroform).

Crystal and Molecular Structure of 1-Benzyl-1,3,3-trimethylazetidinium Iodide

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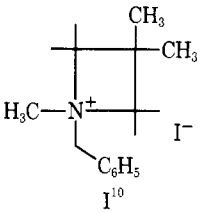
Contribution from the Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122. *Received July 31, 1970*

Abstract: The structure of 1-benzyl-1,3,3-trimethylazetidinium iodide ($C_{13}H_{20}NI$) has been determined by a single-crystal X-ray diffraction study. The compound crystallizes in the orthorhombic space group *Pbca* with eight molecules in a unit cell of dimensions $a = 28.312 \pm 0.005$, $b = 9.653 \pm 0.003$, and $c = 10.474 \pm 0.003$ Å. The azetidinium ring contains N–C distances of 1.52 (2) and 1.52 (2) Å in agreement with other azetidinium rings studied, and C–C distances of 1.54 (2) and 1.57 (2) Å. The ring itself is nonplanar, having a dihedral angle of 169.7°. A final value of $R = 0.038$ was obtained for the 677 statistically significant reflections.

Although azetidinium derivatives were first synthesized and characterized over 8 years ago,[1] they remained a relatively unstudied series of compounds for 50 years. Interest in these compounds was revived when it was shown that the antibiotics penicillin[2] and Cephalosporin C[3] both contain a β-lactam ring. Further interest was generated when azetidine compounds were postulated as possible alkylating agents in the fight against cancer.[4]

Molecular parameters for two unfused azetidinium salts[5,6] appeared for the first time in 1968. These were followed by the structure determination of the first fused ring structure containing an azetidinium ring rather than a β-lactam ring.[7] Finally, the structures of two substituted azetidinium compounds, one containing a planar azetidine ring[8] and the other a nonplanar azetidine ring,[9] were reported in 1969.

Crystal Data. A crystalline sample of the compound 1-benzyl-1,3,3-trimethylazetidinium iodide[10] (I) was kindly furnished by Professor A. G. Anderson, Jr.



I[10]

The compound crystallized in regular needles with the 001 axis parallel to the needle axis. The crystal symmetry is orthorhombic, and a series of precession photographs indicated the following systematic absences: $0kl$, $k = 2n + 1$; $h0l$, $l = 2n + 1$; $hk0$, $h = 2n + 1$, unambiguously determining the space group as *Pbca* (No. 61). The lattice constants were determined by a least-squares fit[11] of 23 reflections whose values were measured very carefully at fine conditions (1° take-off angle and 0.05° receiving slit on a G.E. XRD-5 diffractometer). The resulting lattice constants are: $a = 28.312 \pm 0.005$, $b = 9.653 \pm 0.003$, and $c = 10.474 \pm 0.003$ Å. The calculated density of 1.497 g/cm³ (assuming eight molecules per unit cell) agreed with the experimental density of 1.50 g/cm³, measured by flotation methods.

A crystal was mounted along the 00*l* axis. A preliminary data set was collected on a G.E. XRD-490 automated diffractometer using Cu Kα radiation and balanced filters. Although a polar plot indicated an extremely large absorption correction, it was felt that the data would be suitable for determining a trial structure. Subsequently, a new set of data was measured

(1) S. Gabriel and T. Weiner, *Ber.*, **21**, 2669 (1888).
(2) H. T. Clarke, *et al.*, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.
(3) D. Crowfoot-Hodgkin and E. M. Maslen, *Biochem. J.*, **79**, 393 (1961).
(4) R. B. Ross, *J. Chem. Educ.*, **36**, 368 (1959).
(5) C. L. Moret and L. M. Trefonas, *J. Heterocycl. Chem.*, **5**, 149 (1968).
(6) H. M. Berman, E. L. McGandy, J. W. Burgner, II, and R. L. Van Etten, *J. Amer. Chem. Soc.*, **91**, 6177 (1969).
(7) R. Majeste and L. M. Trefonas, *J. Heterocycl. Chem.*, **5**, 663 (1968).
(8) R. L. Snyder, E. L. McGandy, R. L. Van Etten, L. M. Trefonas, and R. L. Towns, *J. Amer. Chem. Soc.*, **91**, 6187 (1969).
(9) E. L. McGandy, H. M. Berman, J. W. Burgner, III, and R. L. Van Etten, *ibid.*, **91**, 6173 (1969).
(10) A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.*, **33**, 3046 (1968).
(11) Program LSLAT, K. N. Trueblood: a program of least-squares 2θ values of a given set of reflections to determine the best fit of lattice constants.