76. Protolytic Opening of Two Diastereoisomeric Cyclopropanols[1])

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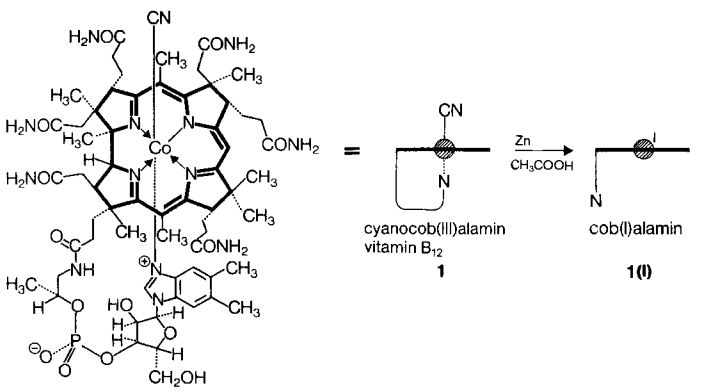
Summary

Cob(I)alamin (**1(I)**)-catalyzed reduction of the aldehyde **2** led to the two crystalline cyclopropanols **3** and **4** (see *Scheme 2*). The protolytic ring-opening starting from **3** produced the saturated aldehydes **6** and **7**; **8** was formed in traces only (see *Scheme 3*). The protolysis starting from **3** led, therefore, mainly to retention of configuration at the spiro C-atom (**7**); ring-opening with inversion was observed in traces only (**8**). Starting from **4**, the protolysis produced **9** and **7**; the absence of **8** showed this protolysis to proceed exclusively with inversion of configuration at the spiro center. Of the *p*-bromobenzoate **5** *(cf. Scheme 2)* the structure has been determined by X-ray analysis.

1. Preparation of 3 and 4. – Using catalytic amounts of cob(I)alamin (**1(I)**; see *Scheme 1*), metallic Zn to regenerate **1(I)** after a catalytic cycle and glacial AcOH as solvent, the aldehyde **2**[2]) was reduced to a mixture from which 11 compounds could be

Scheme 1

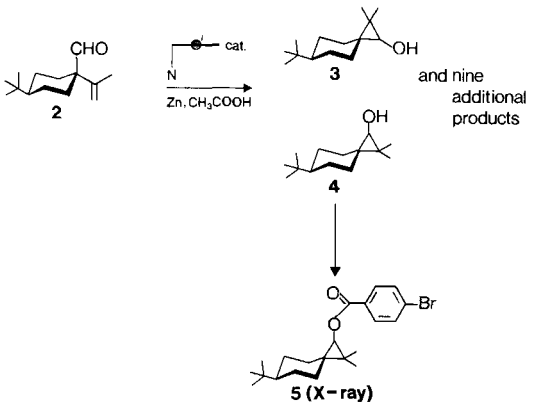


[1]) 12th Communication in the series 'Cob(I)alamin as Catalyst'; for the 11th communication see [1a].

[2]) For the preparation and characterization of **2**, see [1a].

isolated adding up to a total yield of 85.7% after chromatography (see *Scheme 2*)[3]). The two main products could be isolated in 24.8% (**3**) and 32.2% (**4**) yield, respectively. Analytical and spectroscopical data strongly favored diastereoisomeric cyclopropanol structures for these two crystalline compounds. To prove the relative configuration of **3** and **4**, the diastereoisomer **4** was transformed to the corresponding *p*-bromobenzoate **5**. Single-crystal X-ray structure determination of **5** showed the *tert*-butyl group and the dimethyl-substituted C-atom to occupy equatorial, *i.e. trans*-oriented positions.

Scheme 2



ORD examination of the cyclopropanol **4** revealed it to be optically active. The slight dextrorotatory nature of **4** can be explained assuming a 'close' contact of the aldehyde **2** with **1(I)** during the generation of **4**.

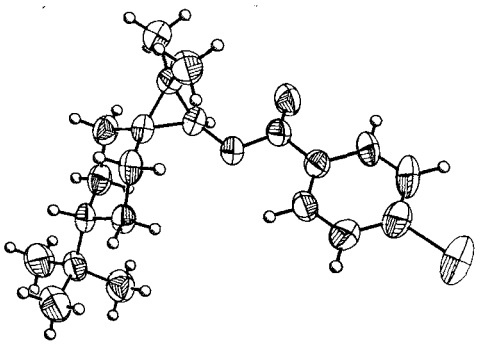


Figure. *Perspective view of* **5** *with 50% probability ellipsoids*

[3]) For details, the isolation of the nine additional products, and the corresponding blank experiments see [1c]. In the literature there are examples of reductive cyclizations leading to acetoxycyclopropanols under more forcing conditions (amalgamated Zn, HCl, Ac_2O) [2] [3].

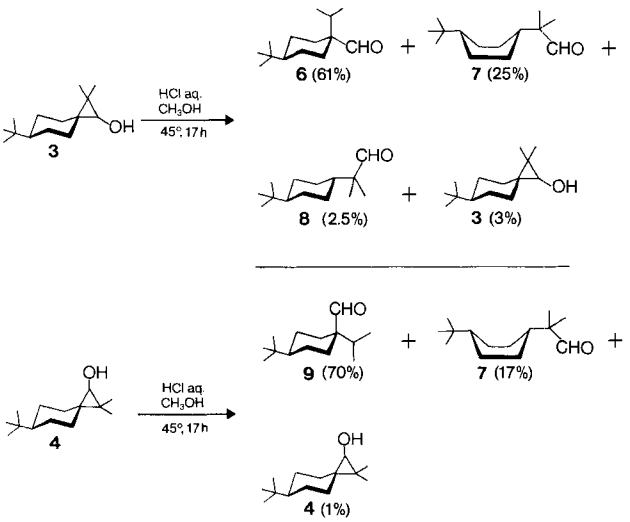
2. X-Ray Analysis of 5.

Crystal Data. $C_{21}H_{29}BrO_2$; mol. wt. 393.37, $F(000) = 412$; crystals from MeOH, m.p. 141 °C. Space group and cell dimensions: triclinic, $P\bar{1}$; $a = 6.883(4)$, $b = 10.232(8)$, $c = 15.283(10)$ Å, $\alpha = 100.41(6)$, $\beta = 100.35(5)$, $\gamma = 100.74(6)°$; $D_{calc.} = 1.29$ Mg·m^{-3}, $z = 2$. $\mu(MoK\alpha) = 2.01$ mm^{-1}, absorption effects ignored.

Data Collection. Crystal size: 0.13 × 0.17 × 0.70 mm^3; temp. 293 °K; $a = 0.71069$ Å. Scan mode: $\theta/2\text{-}\theta$; 6.0°/min minimum scan speed: strong reflections measured at up to 29.30°/min; scan width. 1.8°; $0° \leqslant \theta < 26°$; peak/background ratio: 2:1. Total data measured: 4045; total data observed: 1735; rejection criterion: $I > 2.5 \cdot \sigma(I)$; 217 parameters; weights: $w = 1/(\sigma^2 |Fo| + 0.001 \cdot |Fo|^2)$. Data were collected on a *Nicolet R3m* four-circle diffractometer fitted with a graphite monochromator.

Structure Determination and Refinement. The structure was determined by direct methods. Refinement proceeded smoothly to convergence at $R = 0.059$ with anisotropic refinement of all non-H-atoms. The H-atom coordinates were calculated using known geometries. All calculations were carried out with the SHELXTL [4] package of the *R3m* System.

Scheme 3



3. Protolytic Opening of 3 and 4. – To study the protolytic opening, the two cyclopropanols **3** and **4** were treated with aqueous HCl using MeOH as solvent during 17 h at 45° (see *Scheme 3*). Starting from **3**, products resulting after electrophilic attack of a proton on both C,C single bonds linking the carbinol C-atom to the hydrocarbon skeleton have been observed. The main product was the new aldehyde **6** (61%). Analytical and spectroscopical data showed this aldehyde to be a stereoisomer of **9** [1a]. Taking into account that **6** is produced by protolysis of the cyclopropanol **3**, the *tert*-butyl and isopropyl group must be arranged in a *cis*-relationship. The aldehyde **7** [1a], produced after ring opening following retention of configuration at the spiro C-atom, was obtained in 25% yield. The isomer **8** [1a], resulting from inversion of configuration was produced in traces (2.5%) only. In the literature there is a representative number of examinations studying the stereochemical mode of electrophilic attack on cyclo-

propanols[4]). Exclusive retention, in some cases exclusive inversion, as well as both stereochemical pathways have been observed.

Starting from **4**, the two isomers **9** (70%) and **7** (17%) have been isolated; *i.e.* during attack at the spiro C-atom, this protolysis exclusively follows inversion.

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Experimental Part

General Remarks. See [1a]. The cobalamin-catalyst was prepared according to [1b].

A. Cyclopropanols 3 and 4. – From 3.25 g (0.1 mol-equiv.) of cyanocob(III)alamin (**1**) the catalyst was prepared according to [1b]. To the suspension of the catalyst, dissolved in 400 ml of AcOH and 31.4 g of activated granular Zn (20 mol-equiv.) were added 5.0 g of **2**[5]) in 60 ml of AcOH. The suspension was stirred in the dark at r.t. for 18 h under Ar. After aq. extraction (Et_2O), the crude mixture (5.0 g) was separated by chromatography (SiO_2, Et_2O/hexane). Two crystalline cyclopropanols were isolated as main products: 1.25 g (24.8%) of **3** and 1.62 g (32.2%) of **4**. Moreover, starting material and 8 additional products were detected[3]). 'trans'-*6-(*tert-*Butyl)-2,2-dimethylspiro[2.5]octan-1-ol* (**3**): m.p. 108–109° (hexane), R_f 0.22 (CH_2Cl_2/hexane 2:1), t_R (GC, 100→300°) 10.5 min, $[\alpha]^{r.t.} = 0°(589), 0°(578), +0.3°(546), +0.5°(436), +0.4°(365)$; 0.01 g/ml, EtOH). IR (KBr): 3306 (OH); 1476, 1364, 1143, 1070. ^{1}H-NMR: 0.86 (*s*, 9H, $(CH_3)_3C$); 0.86–1.85 (*m*, 10H, $4CH_2$, CH, OH); 1.07 (*s*, 3H, CH_3–C(2)); 1.12 (*s*, 3H, CH_3–C(2)); 2.84 (*s*, 1H, H–C(1)). ^{13}C-NMR (100.62 MHz): 14.97, 20.99 (2*q*, $(CH_3)_2C$); 22.27, 28.92 (2*s*, C(1), C(8)); 26.44, 26.56, 26.93, 31.95 (4*t*, C(2), C(3), C(5), C(6)); 27.60 (3*q*, $(CH_3)_3C$); 32.46 (*s*, $(CH_3)_3C$); 48.77 (*d*, C(4)); 63.46 (*d*, C(7)). MS: 210 (25, M^+), 195 (11, $M^+ - CH_3$), 111 (100, $M^+ - (CH_3)_2C - (CH_3)_3C$), 57 (84, $(CH_3)_3C^+$).

'cis'-*6-(*tert-*butyl)-2,2-dimethylspiro[2.5]octan-1-ol* (**4**): m.p. 97–99° (hexane), R_f 0.37 (CH_2Cl_2/hexane 2:1), t_R (GC, 100→300°) 9.8 min. IR (KBr): 3339 (OH); 1469, 1445, 1364, 1140, 1099. ^{1}H-NMR: 0.85 (*s*, 9H, $(CH_3)_3C$); 0.85–1.85 (*m*, 9H, $4CH_2$, CH); 0.96 (*s*, 3H, CH_3–C(2)); 0.99 (*s*, 3H, CH_3–C(2)); 1.53 (*s*, 1H, OH); 2.86 (*s*, 1H, H–C(1)). ^{13}C-NMR (100.62 MHz): 14.53, 20.55 (2*q*, $(CH_3)_2C$); 22.24, 28.41 (2*s*, C(1), C(8)); 25.33, 26.57, 27.23, 31.25 (4*t*, C(2), C(3), C(5), C(6)); 27.63 (3*q*, $(CH_3)_3C$); 32.40 (*s*, $(CH_3)_3C$); 48.02 (*d*, C(4)); 63.03 (*d*, C(7)). MS: 210 (16, M^+), 195 (9, $M^+ - CH_3$), 135 (7), 123 (10), 111 (81, $M^+ - (CH_3)_2C - (CH_3)_3C$), 93 (25), 83 (29), 72 (34), 57 (100, $(CH_3)_3C^+$), 43 (43).

B. *p*-Bromobenzoate 5. – To a solution of 86.5 mg of **4** in 4 ml of CH_2Cl_2 and 0.2 ml of Et_3N were added 108 mg of *p*-bromobenzoyl chloride and 7 mg of 4-(dimethylamino)pyridine. The mixture was stirred at r.t. for 18 h. After aq. workup (Et_2O) and chromatographic purification (SiO_2, Et_2O/hexane), 127.5 mg (78.8%) of 'cis'-*6-(*tert-*butyl)-2,2-dimethylspiro[2.5]oct-1-yl-*p-*bromobenzoate* (**5**) were obtained. Crystals for X-ray analysis were grown from hot MeOH, m.p. 141°, R_f 0.57 (Et_2O/hexane 1:4), t_R (GC, 50→330°) 34 min. IR (KBr): 1718 (C=O); 1589, 1481 (arom.); 1396, 1364, 1267, 844, 757. ^{1}H-NMR: 0.85 (*s*, 9H, $(CH_3)_3C$); 0.85–1.90 (*m*, 9H, $4CH_2$, CH); 1.03 (*s*, 3H, CH_3–C(2)); 1.14 (*s*, 3H, CH_3–C(2)); 3.76 (*s*, 1H, H–C(1)); 7.49–7.67 (*m*, 2 arom. H); 7.78–7.97 (*m*, 2 arom. H). MS: 394/392 (0.3/0.3, M^+), 337/335 (0.4/0.4, $M^+ - (CH_3)_3C$), 192 (100, $M^+ - BrC_6H_4COOH$), 185/183 (91/92, $BrC_6H_4CO^+$), 157/155 (25/26), 135 (52, $M^+ - BrC_6H_4COOH - (CH_3)_3C$), 121 (41), 108 (30), 93 (34), 81 (30), 69 (48), 57 (89, $(CH_3)_3C^+$), 43 (83).

C. Protonolysis of 3 and 4. – a) *Starting from* **3**. To 29.1 mg of crystalline **3** in 5 ml of MeOH and 1.5 ml of H_2O were added 1.5 ml of conc. aq. HCl. The solution was stirred at 45° for 17 h under Ar. After neutralization (aq. NaOH) and extraction (Et_2O), the mixture was purified by chromatography (SiO_2, Et_2O/hexane; the 3 aldehydes were eluted as 1 fraction): 17.8 mg (61%) of **6**, 7.3 mg (25%) of **7**, 0.7 mg (2.5%) of **8**, 0.9 mg (3%) of **3**. Data of **7** and **8**: *cf.* [1a]. *4β-(*tert-*Butyl)-1β-isopropylcyclohexanecarboxaldehyde* (**6**): R_f 0.39 (CH_2Cl_2/hexane 1:1), t_R (GC, 50→200°) 20.9 min (under identical GC conditions, the isomeric **9** showed a t_R of 19.9 min).

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[4]) For review articles, *cf.* [5] [6].

[5]) For the data of **2**, *cf.* [1a].

IR (liq.): 1698 (C=O); 1468, 1363. ^{1}H-NMR: 0.85 (*s*, 9H, $(CH_3)_3C$); 1.0 (*d*, $J = 6$, 6H, $(CH_3)_2CH$); 0.85–2.2 (*m*, 10H, $4CH_2$, 2CH); 9.64 (*s*, 1H, CHO). MS: 210 (1, M^+), 181 (9, $M^+ - CHO$), 125 (47, $M^+ - CHO - CH_2 = C(CH_3)_2$), 69 (63), 57 (100, $(CH_3)_3C^+$).

b) *Starting from* **4**. As in *C.a)*, with 53.4 mg of crystalline **4** in 5 ml of MeOH/1.5 ml of H_2O and 1.5 ml of conc. aq. HCl. Chromatography (SiO_2, Et_2O/hexane; the 2 aldehydes were eluted as 1 fraction): 37,4 mg (70%) of **9**, 9.1 mg (17%) of **7**, 0.5 mg (1%) of **4**. Data of **7** and **9**: *cf.* [1a].

D. X-Ray Analysis of 5.

Table 1. *Atom Coordinates (× 10^4) and Temperature Factors ($Å^2$ × 10^3)*

Atom	*x*	*y*	*z*	U^a)
Br(1)	7176 (1)	8577 (1)	5876 (1)	110 (1)
C(1)	8485 (8)	1945 (5)	1398 (3)	50 (2)
C(2)	6301 (8)	1855 (5)	1445 (4)	58 (2)
C(3)	5580 (8)	846 (5)	2002 (4)	55 (2)
C(4)	5909 (8)	−572 (5)	1656 (3)	54 (2)
C(5)	8124 (9)	−451 (5)	1635 (4)	62 (3)
C(6)	8867 (9)	542 (5)	1079 (4)	64 (3)
C(7)	10112 (8)	2907 (5)	2126 (3)	55 (2)
C(8)	9740 (8)	3201 (5)	1195 (4)	57 (2)
O(9)	9411 (5)	3725 (3)	2828 (2)	60 (2)
C(10)	10785 (8)	4881 (5)	3307 (4)	59 (2)
O(11)	12490 (6)	5155 (4)	3231 (3)	87 (2)
C(12)	9848 (8)	5724 (5)	3941 (3)	57 (2)
C(13)	7858 (9)	5372 (5)	4004 (4)	61 (2)
C(14)	7063 (9)	6206 (6)	4585 (4)	67 (3)
C(15)	8258 (11)	7404 (6)	5103 (4)	69 (3)
C(16)	10232 (12)	7776 (7)	5056 (4)	87 (3)
C(17)	11045 (10)	6956 (6)	4475 (4)	76 (3)
C(18)	8759 (9)	4366 (6)	1038 (4)	75 (3)
C(19)	11364 (9)	3051 (7)	665 (4)	78 (3)
C(20)	5050 (9)	−1662 (6)	2159 (4)	63 (3)
C(21)	5421 (11)	−3052 (6)	1766 (5)	96 (4)
C(22)	2771 (10)	−1808 (7)	2049 (5)	90 (3)
C(23)	6017 (10)	−1292 (6)	3182 (4)	81 (3)

a) Equivalent isotropic *U* defined as ⅓ of the trace of the orthogonalized U_{ij} tensor.

Table 2. *Bond Lengths (Å)*

Bond	Length	Bond	Length
Br(1)–C(15)	1.879 (7)	C(1)–C(2)	1.504 (8)
C(1)–C(6)	1.517 (8)	C(1)–C(7)	1.485 (6)
C(1)–C(8)	1.524 (8)	C(2)–C(3)	1.522 (8)
C(3)–C(4)	1.524 (8)	C(4)–C(5)	1.513 (8)
C(4)–C(20)	1.554 (8)	C(5)–C(6)	1.513 (9)
C(7)–C(8)	1.495 (8)	C(7)–O(9)	1.448 (7)
C(8)–C(18)	1.509 (9)	C(8)–C(19)	1.507 (9)
O(9)–C(10)	1.361 (5)	C(10)–O(11)	1.186 (7)
C(10)–C(12)	1.492 (8)	C(12)–C(13)	1.375 (8)
C(12)–C(17)	1.391 (7)	C(13)–C(14)	1.375 (9)
C(14)–C(15)	1.359 (7)	C(15)–C(16)	1.359 (11)
C(16)–C(17)	1.375 (10)	C(20)–C(21)	1.526 (9)
C(20)–C(22)	1.523 (9)	C(20)–C(23)	1.533 (8)

Table 3. *Bond Angles (deg.)*

Angle	Degrees	Angle	Degrees
C(2)–C(1)–C(6)	111.1 (4)	C(2)–C(1)–C(7)	119.8 (5)
C(6)–C(1)–C(7)	116.0 (5)	C(2)–C(1)–C(8)	121.0 (5)
C(6)–C(1)–C(8)	120.5 (5)	C(7)–C(1)–C(8)	59.6 (3)
C(1)–C(2)–C(3)	112.3 (5)	C(2)–C(3)–C(4)	112.5 (5)
C(3)–C(4)–C(5)	108.7 (4)	C(3)–C(4)–C(20)	114.3 (5)
C(5)–C(4)–C(20)	114.4 (5)	C(4)–C(5)–C(6)	112.9 (5)
C(1)–C(6)–C(5)	112.2 (5)	C(1)–C(7)–C(8)	61.5 (3)
C(1)–C(7)–O(9)	115.1 (5)	C(8)–C(7)–O(9)	117.6 (5)
C(1)–C(8)–C(7)	58.9 (3)	C(1)–C(8)–C(18)	119.0 (5)
C(7)–C(8)–C(18)	119.2 (5)	C(1)–C(8)–C(19)	119.9 (5)
C(7)–C(8)–C(19)	116.4 (5)	C(18)–C(8)–C(19)	113.1 (5)
C(7)–O(9)–C(10)	114.6 (4)	O(9)–C(10)–O(11)	124.0 (5)
O(9)–C(10)–C(12)	110.4 (5)	O(11)–C(10)–C(12)	125.6 (4)
C(10)–C(12)–C(13)	123.8 (4)	C(10)–C(12)–C(17)	117.8 (5)
C(13)–C(12)–C(17)	118.4 (5)	C(12)–C(13)–C(14)	121.2 (5)
C(13)–C(14)–C(15)	119.6 (6)	Br(1)–C(15)–C(14)	120.1 (6)
Br(1)–C(15)–C(16)	119.4 (4)	C(14)–C(15)–C(16)	120.5 (6)
C(15)–C(16)–C(17)	120.6 (5)	C(12)–C(17)–C(16)	119.8 (6)
C(4)–C(20)–C(21)	110.9 (5)	C(4)–C(20)–C(22)	109.9 (5)
C(21)–C(20)–C(22)	108.0 (5)	C(4)–C(20)–C(23)	112.3 (4)
C(21)–C(20)–C(23)	107.6 (5)	C(22)–C(20)–C(23)	108.0 (5)

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