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Crystal structure of 2-bromo-1′-$\alpha\beta$-dehydro-ergokryptam acetone sesquisolvate, $C_{32}H_{38}BrN_5O_4 \cdot 1.5(CH_3)_2CO$

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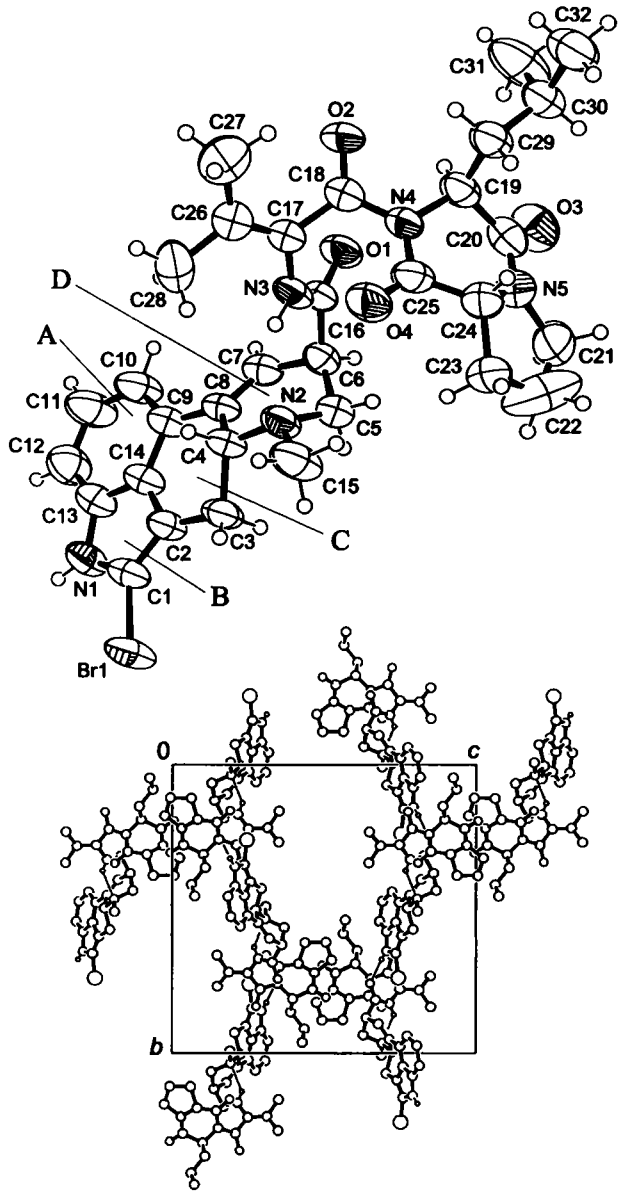

Abstract

$C_{36.50}H_{46}BrN_5O_{5.50}$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 9.771(3)$ Å, $b = 19.853(2)$ Å, $c = 20.763(3)$ Å, $V = 4027.7$ Å^3, $Z = 4$, $R_{gt}(F) = 0.046$, $wR_{ref}(F) = 0.056$, $T = 293$ K.

Source of material

α-Ergokryptine (5.7 g, 10 mmol) was dissolved in mixture of 50 ml dichloromethane and 50 ml 1,4-dioxane, and 2,2′-azobis(2-methylpropionitrile) (100 mg, Fluka) was added. The solution was stirred at 50 °C (temperature of the bath) and pyrrolidone hydrotribromide (7.44 g, 15 mmol, Aldrich) dissolved in 50 ml dichloromethane and 50 ml 1,4-dioxane was added within about 30 minutes. After 3 hours of stirring at 50 °C, the reaction mixture was diluted with 200 ml dichloromethane and 200 ml of 2 % aqueous solution of sodium carbonate was added. The phases were separated and the organic phase was concentrated obtaining thus 10.3 g of brown oil, containing besides 28 % of 2-bromo-α-ergokryptine, 56 % and 6 % of two unknown compounds. The oil was dissolved in dichloromethane and chromatographed on a silica gel using dichloromethane as the mobile phase. The fractions, which did not contained 2-bromo-α-ergokryptine, were pooled and evaporated to dryness obtaining thus a yellow solid foam (3.1 g), containing 82.5 % and 8.7 % of two side products. Single crystals of major 2-bromo-1′-$\alpha\beta$-dehydro-ergokryptam (systematic name *N*-(2-bromo-D-lysergyl-$\alpha\beta$-dehydrovalyl)-*cyclo*(L-leucyl-D-prolyl))were obtained directly by partial evaporation of a saturated solution of its 82.5 % concentrate in acetone (65 mg/3 ml) at ambient temperature (298 K).

Experimental details

Two cavities of volumes 595 Å^3 are filled with disordered acetone in the unit cell. Since disorder models gave unsatisfactory results, the contribution of the disordered solvent to the scattering factors has been taken into account with PLATON/SQUEEZE [1,2]. 92 e^- were found in each cavity, corresponding to approximately three acetone molecules per cavity. Single crystals of bromokryptam were obtained by chance some time ago and we have succeeded with the crystal structure determination. NMR of one of single crystals dissolved in chloroform-*d*3 revealed the presence of acetone, which was considered in the refinement. We are well aware that it would be much better to repeat the crystal structure determination at low temperature. Accordingly we tried several times to prepare new crystals, but since that time, crystals of suitable quality have not been obtained. Most probably, high degree of conformation freedom, low stability in solution and limited material available to refine the conditions for crystallization had hampered the formation of a single crystals. Since the substance is rather unusual and serves as well as a proof of yet unknown reaction of ergot alkaloids, we believe that it would be pity to keep it hide-and-seek.

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Discussion

Ergot alkaloids of peptidic type are widely used in the therapy (e.g., bromokryptine mesylate, ergotamine tartrate, dihydroergotamine mesylate, dihydroergotoxine mesylate) and therefore no wonder that considerable effort has been devoted to their degradation products as possible impurities of the used drugs.

Crystal structure determination revealed that the compound corresponds in fact to the 2-brominated and 1′-$\alpha\beta$-dehydro analogue of α-ergokryptam (figure, top) [3,4]. The 2-bromination of α-ergokryptine was accompanied by the opening of cyclol ring, dehydration of valine to $\alpha\beta$-dehydrovaline, and finally, by the epimerization of L-proline to D-proline. Apparently, *trans*-diketopiperazine is thermodynamically favored [5], and thus *cis*-diketopiperazine lactam (containing L-proline) is the minor component in the reaction mixture. The ergoline A and B rings, forming the indole moiety, are nearly planar (χ^2 test values are 5.85 and 3.72, respectively). The dihedral angle between these two planes is 1.91(8)°. Ring C (C2, C3, C4, C8, C9, C14) possesses E_3 conformation (puckering parameters according to Cremer and Pople are $Q = 0.464(4)$ Å, $\varphi = -60.8(7)°$, $\theta = 126.3(5)°$). Conformation of ring D (N2, C4, C8, C7, C6, C5) lies between $^1H_6$ and E_6 ($Q = 0.507(3)$ Å, $\varphi = -43.5(5)°$, $\theta = 53.0(4)°$). This conformation of the ring D can be found in ergopeptine bases crystallized from non-polar solvents [15,16], is usually denominated as *CB* or flap down conformation [17], and differs from that one found in bromokryptine mesylate or ergopeptine alkaloids crystallized from aqueous solvents (*E* or flap up) [18,19]. The torsion angles about the C/D ring junction C3–C4–C8–C7 and N2–C4–C8–C9 are –123.3(4)° and –175.2(3)°, respectively. 2-Bromoergolene moiety is connected via $\alpha\beta$-dehydrovaline to L-Leu-D-Pro diketopiperazine, which conformation is nearly identical with L-Phe-D-Pro diketopiperazine in ergocristam [15]. Diketopiperazine moiety possesses $^{2,5}B$ conformation, $Q = 0.528(4)$ Å, $\varphi = -124.2(4)°$, $\theta = 92.7(4)°$. D-Pro ring has $^5T_4$ conformation, $Q = 0.172(6)$ Å, $\varphi = 124(2)°$. One intramolecular hydrogen bond N3–H···N2 was found in addition to one intermolecular hydrogen bond N1–H511···O1 ($-x+1, y-½, -z+½$) forming an infinite chain of molecules along the *b* axis (figure, bottom).

Table 1. Data collection and handling.

Crystal:	colorless prism, size 0.33 × 0.42 × 0.72 mm
Wavelength:	Cu K_α radiation (1.54180 Å)
μ:	16.67 cm^{-1}
Diffractometer, scan mode:	Enraf-Nonius CAD4, $\omega/2\theta$
$2\theta_{max}$:	110.02°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	4951, 5834
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 4405
$N(param)_{refined}$:	380
Programs:	PLATON [1], SIR92 [11], CRYSTALS [12], ORTEP-3 [13]

Table 2. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	*x*	*y*	*z*	U_{iso}
H(31)	4*a*	0.3222	0.4253	0.3412	0.088
H(32)	4*a*	0.2251	0.4008	0.2817	0.088
H(41)	4*a*	0.2565	0.5041	0.2285	0.077
H(51)	4*a*	0.1059	0.5793	0.3906	0.092
H(52)	4*a*	0.2381	0.5295	0.3977	0.092
H(61)	4*a*	0.3219	0.6372	0.4041	0.083
H(71)	4*a*	0.4923	0.6298	0.3219	0.081
H(101)	4*a*	0.6409	0.6091	0.2317	0.112
H(111)	4*a*	0.8183	0.5543	0.1744	0.132
H(121)	4*a*	0.8236	0.4340	0.1617	0.117
H(151)	4*a*	–0.0377	0.5164	0.3321	0.117

Table 2. Continued.

Atom	Site	*x*	*y*	*z*	U_{iso}
H(152)	4*a*	0.0590	0.4493	0.3331	0.117
H(153)	4*a*	0.0074	0.4807	0.2646	0.117
H(191)	4*a*	0.0087	0.8404	0.3920	0.080
H(211)	4*a*	–0.1737	0.6973	0.5616	0.144
H(212)	4*a*	–0.0269	0.6671	0.5376	0.144
H(221)	4*a*	–0.2764	0.6096	0.5316	0.215
H(222)	4*a*	–0.1276	0.5763	0.5152	0.215
H(231)	4*a*	–0.3174	0.6005	0.4305	0.136
H(232)	4*a*	–0.1567	0.5872	0.4131	0.136
H(241)	4*a*	–0.3007	0.7107	0.4162	0.096
H(271)	4*a*	–0.0810	0.8038	0.1792	0.154
H(272)	4*a*	0.0110	0.7895	0.1149	0.154
H(273)	4*a*	–0.1257	0.7441	0.1288	0.154
H(281)	4*a*	0.0760	0.6661	0.1013	0.141
H(282)	4*a*	0.2015	0.6602	0.1530	0.141
H(283)	4*a*	0.0608	0.6174	0.1643	0.141
H(291)	4*a*	–0.1990	0.8751	0.3459	0.092
H(292)	4*a*	–0.2817	0.8285	0.3977	0.092
H(301)	4*a*	–0.2052	0.8979	0.4813	0.106
H(311)	4*a*	–0.0943	1.0005	0.4612	0.172
H(312)	4*a*	–0.0832	0.9805	0.3850	0.172
H(313)	4*a*	0.0017	0.9373	0.4388	0.172
H(321)	4*a*	–0.3424	0.9943	0.4556	0.136
H(322)	4*a*	–0.3399	0.9722	0.3798	0.136
H(323)	4*a*	–0.4176	0.9248	0.4328	0.136
H(511)	4*a*	0.6654	0.3252	0.1899	0.050
H(531)	4*a*	0.1162	0.6326	0.2690	0.050

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(1)	4*a*	0.40162(5)	0.26082(2)	0.24533(3)	0.1200(4)	0.0386(2)	0.1461(4)	–0.0001(2)	–0.0010(3)	–0.0124(2)
N(1)	4*a*	0.6029(4)	0.3534(2)	0.2063(2)	0.078(2)	0.052(2)	0.110(2)	0.012(2)	0.007(2)	–0.017(2)
N(2)	4*a*	0.1607(3)	0.5347(1)	0.3073(2)	0.074(2)	0.043(2)	0.092(2)	–0.004(1)	0.012(2)	–0.011(2)
N(3)	4*a*	0.1314(3)	0.6722(1)	0.2833(2)	0.093(2)	0.039(2)	0.079(2)	0.004(1)	–0.001(2)	–0.013(1)
N(4)	4*a*	–0.0671(3)	0.7589(1)	0.3463(1)	0.073(2)	0.040(2)	0.074(2)	0.001(1)	0.008(1)	–0.004(1)
N(5)	4*a*	–0.1268(4)	0.7205(2)	0.4689(2)	0.108(3)	0.071(2)	0.082(2)	0.015(2)	0.017(2)	0.012(2)
O(1)	4*a*	0.2471(3)	0.7426(1)	0.3479(1)	0.096(2)	0.044(1)	0.100(2)	–0.008(1)	0.007(1)	–0.011(1)
O(2)	4*a*	0.0153(3)	0.8372(1)	0.2765(2)	0.125(2)	0.041(2)	0.107(2)	0.007(1)	0.027(2)	0.012(1)
O(3)	4*a*	0.0014(3)	0.8054(2)	0.5062(2)	0.109(2)	0.106(3)	0.104(2)	0.008(2)	–0.021(2)	–0.019(2)
O(4)	4*a*	–0.1533(3)	0.6593(1)	0.3098(1)	0.106(2)	0.053(2)	0.101(2)	–0.016(1)	0.007(2)	–0.015(2)

Table 3. Continued.

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	4*a*	0.4806(4)	0.3462(2)	0.2371(2)	0.091(3)	0.039(2)	0.094(3)	0.004(2)	−0.013(2)	−0.008(2)
C(2)	4*a*	0.4306(4)	0.4062(2)	0.2578(2)	0.079(2)	0.040(2)	0.086(2)	0.004(2)	0.001(2)	−0.006(2)
C(3)	4*a*	0.3056(4)	0.4292(2)	0.2938(2)	0.085(2)	0.039(2)	0.101(3)	0.002(2)	0.012(2)	−0.004(2)
C(4)	4*a*	0.2781(4)	0.5037(2)	0.2755(2)	0.072(2)	0.035(2)	0.083(2)	−0.000(1)	−0.005(2)	−0.005(1)
C(5)	4*a*	0.1928(5)	0.5640(2)	0.3698(2)	0.107(3)	0.052(2)	0.077(2)	0.000(2)	0.012(2)	−0.002(2)
C(6)	4*a*	0.2871(4)	0.6236(2)	0.3607(2)	0.099(3)	0.048(2)	0.066(2)	−0.003(2)	0.001(2)	−0.010(2)
C(7)	4*a*	0.4070(4)	0.6019(2)	0.3206(2)	0.076(2)	0.048(2)	0.081(2)	−0.003(2)	−0.009(2)	−0.001(2)
C(8)	4*a*	0.4053(4)	0.5477(2)	0.2837(2)	0.072(2)	0.039(2)	0.076(2)	−0.001(2)	−0.006(2)	−0.003(2)
C(9)	4*a*	0.5264(4)	0.5234(2)	0.2488(2)	0.075(2)	0.043(2)	0.092(2)	0.000(2)	−0.008(2)	−0.010(2)
C(10)	4*a*	0.6364(4)	0.5593(2)	0.2249(3)	0.078(3)	0.049(2)	0.150(4)	−0.004(2)	0.012(2)	−0.004(2)
C(11)	4*a*	0.7427(5)	0.5265(2)	0.1932(3)	0.080(3)	0.066(3)	0.184(5)	−0.007(2)	0.022(3)	−0.005(3)
C(12)	4*a*	0.7453(5)	0.4569(2)	0.1837(3)	0.081(3)	0.083(3)	0.134(4)	0.005(2)	0.018(3)	−0.011(3)
C(13)	4*a*	0.6362(4)	0.4215(2)	0.2070(2)	0.076(3)	0.053(2)	0.094(3)	0.014(2)	−0.007(2)	−0.010(2)
C(14)	4*a*	0.5296(4)	0.4533(2)	0.2381(2)	0.075(2)	0.044(2)	0.091(3)	0.009(2)	−0.012(2)	−0.008(2)
C(15)	4*a*	0.0374(4)	0.4918(2)	0.3094(3)	0.077(2)	0.056(2)	0.161(5)	−0.005(2)	0.020(3)	−0.016(3)
C(16)	4*a*	0.2183(4)	0.6849(2)	0.3299(2)	0.083(2)	0.039(2)	0.072(2)	0.001(2)	0.016(2)	−0.005(2)
C(17)	4*a*	0.0581(4)	0.7221(2)	0.2493(2)	0.092(2)	0.047(2)	0.074(2)	0.008(2)	0.013(2)	0.001(2)
C(18)	4*a*	0.0012(4)	0.7777(2)	0.2897(2)	0.093(3)	0.050(2)	0.083(3)	0.007(2)	0.010(2)	−0.003(2)
C(19)	4*a*	−0.0738(4)	0.8112(2)	0.3973(2)	0.081(2)	0.046(2)	0.084(2)	−0.002(2)	0.003(2)	−0.013(2)
C(20)	4*a*	−0.0641(4)	0.7788(2)	0.4626(2)	0.074(2)	0.073(3)	0.084(3)	0.017(2)	−0.003(2)	−0.016(2)
C(21)	4*a*	−0.1237(8)	0.6762(3)	0.5248(2)	0.165(5)	0.108(4)	0.087(3)	0.048(4)	0.024(3)	0.017(3)
C(22)	4*a*	−0.1901(8)	0.6151(4)	0.5063(5)	0.137(5)	0.146(7)	0.24(1)	−0.028(5)	−0.037(6)	0.117(7)
C(23)	4*a*	−0.2216(7)	0.6164(2)	0.4377(3)	0.143(4)	0.062(3)	0.127(4)	0.007(3)	0.056(4)	0.020(3)
C(24)	4*a*	−0.2074(5)	0.6900(2)	0.4169(2)	0.095(3)	0.054(2)	0.088(3)	−0.009(2)	0.017(2)	−0.003(2)
C(25)	4*a*	−0.1405(4)	0.6996(2)	0.3528(2)	0.074(2)	0.043(2)	0.089(3)	−0.002(2)	0.002(2)	0.000(2)
C(26)	4*a*	0.0373(5)	0.7189(2)	0.1858(2)	0.111(3)	0.071(3)	0.081(3)	0.010(2)	0.013(2)	0.003(2)
C(27)	4*a*	−0.0464(7)	0.7682(3)	0.1492(3)	0.166(5)	0.119(5)	0.090(3)	0.027(4)	−0.004(3)	0.022(3)
C(28)	4*a*	0.0998(7)	0.6607(3)	0.1479(2)	0.149(4)	0.120(4)	0.079(3)	0.023(4)	0.019(3)	−0.018(3)
C(29)	4*a*	−0.1984(4)	0.8568(2)	0.3907(2)	0.082(2)	0.053(2)	0.094(3)	0.004(2)	0.006(2)	−0.006(2)
C(30)	4*a*	−0.2047(5)	0.9156(2)	0.4362(2)	0.112(3)	0.062(2)	0.088(3)	0.020(2)	0.006(3)	−0.009(2)
C(31)	4*a*	−0.0851(7)	0.9624(3)	0.4300(4)	0.136(4)	0.073(3)	0.226(7)	−0.002(3)	−0.001(5)	−0.058(4)
C(32)	4*a*	−0.3377(6)	0.9553(3)	0.4252(3)	0.129(4)	0.069(3)	0.154(5)	0.023(3)	0.030(3)	−0.006(3)

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