

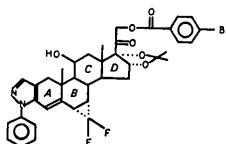
## The Structure of 6 $\alpha$ ,7 $\alpha$ -Difluoromethylene-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-21-*p*-bromobenzoyloxy-pregn-4-en-20-one[3,2-*c*]-2'-phenylpyrazole\*

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(Received 16 February 1970)

The crystal structure of 6 $\alpha$ ,7 $\alpha$ -difluoromethylene-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-21-*p*-bromobenzoyloxy-pregn-4-en-20-one[3,2-*c*]-2'-phenylpyrazole, C<sub>39</sub>H<sub>39</sub>F<sub>2</sub>N<sub>2</sub>O<sub>6</sub>Br has been determined by X-ray diffraction. The compound crystallizes in space group *P*2<sub>1</sub>, *a*=11.532 (0.009), *b*=18.672 (0.020), *c*=9.642 (0.012) Å and  $\beta$ =98.48 (0.05)°. There are two molecules in the unit cell, which also contains two molecules of butanol. The structure was solved by application of the tangent formula to the heavy atom phases and was refined by block-diagonal least squares to a final *R* value of 0.057. The refinement was based on 3201 reflections collected with an automatic diffractometer. The structure corresponds to the formula:

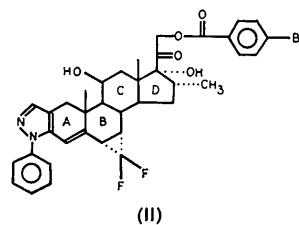
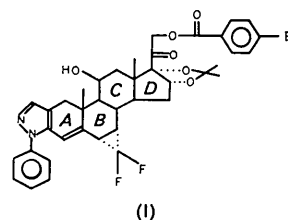


The *A* ring is puckered, the *B* ring is in the half chair conformation and the *D* ring is a slightly distorted  $\alpha$ -envelope.

### Introduction

Although the introduction of a 6 $\alpha$ ,7 $\alpha$ -difluoromethylene group generally potentiates the antiinflammatory activity of various corticoids, the 6 $\alpha$ ,7 $\alpha$ -difluoromethylene-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy corticoids are an exception and show decreased biological activity (Harrison, Beard, Kirkham, Lewis, Jamieson, Rooks & Fried, 1968). It was postulated that the decreased activity is a result of impaired interaction with the receptor site due to conformational distortion of rings *C* and *D* caused by the two large  $\alpha$ -face substituents.

A comparison of the crystal structures of 6 $\alpha$ ,7 $\alpha$ -difluoromethylene-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-21-*p*-bromobenzoyloxy-pregn-4-en-20-one[3,2-*c*]-2'-phenylpyrazole (I) and 6 $\alpha$ ,7 $\alpha$ -difluoromethylene-16 $\alpha$ -methyl-11 $\beta$ ,17 $\alpha$ ,21-trihydroxypregn-4-en-20-one[3,2-*c*]-2'-phenylpyrazole 21-(*p*-bromobenzoate) (II) (Christensen, 1970) appeared to be of value in a further investigation of this supposition, and the present work is part of a study of structure-activity relationships.



### Experimental

The heavy-atom derivative was prepared by Dr Ian Harrison, who also supplied the crystals. Two crystalline modifications were obtained. Preliminary precession photographs indicated orthorhombic symmetry in crystals obtained from acetone, with *a*=16.57, *b*=15.37, *c*=14.64 Å, and space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (from systematic extinctions *h*00, 0*k*0 and 00*l* with *h*, *k* or

\* Contribution No. 376 from the Syntex Institute of Organic Chemistry.

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Table 1. Final positional parameters and their standard deviations

	X	Y	Z
C (1)	0.32859 (55)	-0.78814 (39)	0.63319 (97)
C (2)	0.33237 (58)	-0.86807 (41)	0.66076 (100)
C (3)	0.24252 (52)	-0.90043 (33)	0.70702 (80)
C (4)	0.13271 (49)	-0.86464 (36)	0.72534 (72)
C (5)	0.11814 (46)	-0.79805 (34)	0.67923 (63)
C (6)	0.00608 (44)	-0.76111 (31)	0.69419 (58)
C (7)	-0.01142 (44)	-0.68224 (31)	0.65785 (60)
C (8)	0.08304 (46)	-0.64004 (30)	0.60027 (56)
C (9)	0.20539 (44)	-0.67749 (30)	0.63020 (60)
C (10)	0.20341 (49)	-0.75880 (34)	0.59647 (69)
C (11)	0.29735 (53)	-0.63256 (32)	0.56674 (75)
C (12)	0.30083 (48)	-0.55454 (31)	0.61872 (68)
C (13)	0.18221 (47)	-0.53830 (31)	0.59900 (54)
C (14)	0.09584 (45)	-0.56501 (32)	0.66451 (58)
C (15)	-0.01006 (51)	-0.51802 (34)	0.66721 (73)
C (16)	0.04712 (56)	-0.44885 (36)	0.72512 (68)
C (17)	0.17463 (51)	-0.44942 (32)	0.68972 (60)
C (18)	0.13870 (64)	-0.49720 (50)	0.44404 (60)
C (19)	0.15608 (71)	-0.77481 (45)	0.45959 (84)
C (20)	0.21111 (54)	-0.38061 (32)	0.62206 (63)
O (21)	0.14123 (42)	-0.35688 (25)	0.56491 (52)
C (22)	0.34057 (66)	-0.36819 (44)	0.62832 (93)
O (23)	0.36563 (44)	-0.30115 (27)	0.56653 (56)
C (24)	0.34465 (54)	-0.29998 (38)	0.62405 (73)
O (25)	0.31833 (51)	-0.34998 (30)	0.35378 (66)
C (26)	0.36137 (47)	-0.22716 (37)	0.36998 (65)
C (27)	0.34862 (64)	-0.21659 (56)	0.22621 (79)
C (28)	0.35828 (76)	-0.15243 (67)	0.16661 (84)
C (29)	0.37756 (59)	-0.09389 (39)	0.25360 (85)
C (30)	0.39283 (62)	-0.10205 (35)	0.39908 (82)
C (31)	0.38581 (54)	-0.16910 (35)	0.45470 (70)
BR (32)	0.38473 (10)	0.00000 (0)	0.17910 (15)
O (33)	0.06301 (46)	-0.45070 (29)	0.87451 (50)
O (34)	0.24695 (38)	-0.45529 (22)	0.82288 (40)
C (35)	0.00023 (44)	-0.70624 (32)	0.80157 (60)
F (36)	-0.09446 (31)	-0.70580 (22)	0.86932 (39)
F (37)	0.09544 (30)	-0.69058 (21)	0.89594 (34)
O (38)	0.27094 (51)	-0.63570 (31)	0.41611 (58)
C (39)	0.41679 (73)	-0.91866 (46)	0.65763 (127)
N (40)	0.38009 (52)	-0.98246 (32)	0.69499 (97)
N (41)	0.27182 (48)	-0.97018 (29)	0.72786 (77)
C (42)	0.20199 (57)	-1.02973 (34)	0.76289 (74)
C (43)	0.13522 (69)	-1.02293 (41)	0.87426 (76)
C (44)	0.06759 (78)	-1.07925 (51)	0.90226 (79)
C (45)	0.06825 (82)	-1.14227 (45)	0.85090 (83)
C (46)	0.13559 (71)	-1.14968 (44)	0.72585 (73)
C (47)	0.20192 (61)	-1.09434 (36)	0.69188 (77)
C (48)	0.17679 (78)	-0.42960 (53)	0.62682 (75)
C (49)	0.19718 (114)	-0.34758 (60)	0.94513 (110)
C (50)	0.21749 (120)	-0.47289 (66)	1.05085 (83)
O (51)	0.45419 (120)	0.40471 (66)	0.26282 (85)
C (52)	0.45329 (47)	0.37946 (35)	0.37041 (55)
C (53)	0.37676 (166)	0.31784 (97)	0.09166 (177)
C (54)	0.41539 (275)	0.26555 (172)	0.15081 (347)
C (55)	0.36348 (282)	0.18444 (115)	0.06057 (310)

*l* odd). Crystals from butanol displayed monoclinic symmetry; the systematic extinctions  $0k0$  with  $k$  odd are consistent with space group  $P2_1$ . The orthorhombic crystals were small and of poor quality, and a monoclinic crystal with dimensions of approximately  $0.20 \times 0.20 \times 0.40$  mm was used for determination of cell parameters and collection of intensity data. The cell parameters and direction cosines of the reciprocal axes relative to the instrument coordinate system were refined by least squares. The refinement gave the following results (estimated standard deviations in parentheses):  $a=11.532$  (0.009),  $b=18.672$  (0.020),  $c=9.642$  (0.012) Å and  $\beta=98.48$  (0.05)° ( $\lambda$ Cu  $K\alpha=1.54051$  Å). These values give a calculated density of  $1.19$  g.cm $^{-3}$  for  $Z=2$ . For an additional two molecules of butanol in the unit cell the calculated density is  $1.31$  g.cm $^{-3}$ . The density observed by flotation in an aqueous solution of potassium iodide was  $1.32$  g.cm $^{-3}$ ; the presence of two molecules of butanol thus indicated, was verified by the crystal structure analysis. The linear absorption coefficient for copper radiation is  $20$  cm $^{-1}$ , no correction for absorption was applied.

The intensity data were collected with a Picker automatic diffractometer using Ni-filtered Cu  $K\alpha$  radiation. The intensities of 3658 reflections in the range  $0^\circ < 2\theta < 160^\circ$  were measured using the  $2\theta-\theta$  technique; 3201 which had an intensity greater than three times their e.s.d. were recorded as 'observed'.

Two standard reflections were measured at regular intervals during the course of the data collection. While one of the standard reflections tapered off to  $\sim 85\%$  of the original intensity, the other was more stable and ended up at  $\sim 95\%$  of the original intensity.

### Computing procedures

The least-squares routine for calculating cell dimensions and diffractometer coordinates, the diffractometer setting program, the Lp program and the routine used to calculate the Patterson function are referenced in a previous paper (Hope & Christensen, 1968).

The normalized structure factors were calculated with a routine written by H. S. Maddox. The program for cyclic phase refinement by the tangent formula was that of Brenner & Gum (1970). The structure factors and the Fourier summations were calculated with programs written by B. Klewe. The block-diagonal least-squares routine which is referenced in a previous paper (Christensen, 1970) was revised by H. Hope to include the calculations for incorporating anomalous scattering. The program minimizes the weighted sum of  $(KF_0 - G|F_c|)^2$ . The shifts were given by  $\Delta'q_n = k_1\Delta q_n + k_2\Delta q_{n-1}$ , where  $\Delta q_n$  is the shift called for in the  $n$ th cycle (Sparks, 1961). The values used for  $k_1$  and  $k_2$  were 0.8 and 0.2 respectively, except for the two last cycles where the values 1.0 and 0.0 were used. The weighting scheme used was that of Hughes (1941) with  $4F_0(\min)=10$ .

The atomic form factors were those given by Hanson, Herman, Lea & Skillman (1964).

The anisotropic temperature factors are of the form:

$$\exp [-(h^2B_{11} + k^2B_{22} + l^2B_{33} + hkB_{12} + hlB_{13} + klB_{23})].$$

The  $R$  index defined by  $R = \sum ||F_o| - |F_c|| / \sum |F_o|$  included observed reflections only.

### Determination and refinement of the structure

The position of the Br atom was determined from a sharpened Patterson function (Patterson, 1935), and a weighted Fourier synthesis (Sim, 1960) eventually revealed the approximate orientation of the bromobenzoate moiety. At this stage all reflections with  $E$  (the normalized structure factor)  $\geq 1.5$  were assigned phase angles computed from the bromobenzoate group; weight factors giving a measure of the reliability of the phases were also computed (Sim, 1960). Using the weights and the  $E$  values as criteria 300 reflections were selected. These phases were refined by two cycles of the tangent formula (Karle & Hauptman, 1956). After

Table 2. Final thermal parameters, with e.s.d.'s in parentheses

The anisotropic temperature factor has the form

$$\exp [-\frac{1}{4}(B_{11}h^2a^2 + B_{22}k^2b^2 + B_{33}l^2c^2 + 2B_{12}hka + 2B_{13}hkl + 2B_{23}kbl)]$$

	B <sub>11</sub>	B <sub>22</sub>	B <sub>33</sub>	B <sub>12</sub>	B <sub>13</sub>	B <sub>23</sub>
C (1)	3.10(24)	4.02(31)	9.58(50)	-0.63(22)	2.22(27)	-1.45(31)
C (2)	3.61(26)	4.66(31)	9.83(50)	-0.59(23)	2.43(28)	-1.72(35)
C (3)	5.90(25)	3.16(25)	7.52(39)	0.02(20)	1.67(24)	-1.39(24)
C (4)	3.41(25)	4.21(27)	6.04(30)	0.09(19)	1.20(20)	-0.66(25)
C (5)	3.11(20)	4.37(27)	4.41(25)	-0.62(19)	1.10(17)	-1.55(21)
C (6)	3.07(20)	3.50(21)	4.50(24)	-0.39(17)	0.90(17)	-0.42(19)
C (7)	3.13(20)	3.66(25)	4.06(25)	-0.28(18)	0.53(17)	-0.31(19)
C (8)	3.58(21)	3.50(22)	3.60(20)	-0.79(16)	0.78(17)	-0.67(18)
C (9)	3.27(20)	3.12(21)	4.70(24)	-0.75(17)	1.08(18)	-0.93(18)
C (10)	3.70(23)	3.60(23)	5.81(30)	-0.87(19)	1.89(21)	-1.27(25)
C (11)	4.19(24)	3.18(22)	6.77(34)	-1.19(20)	2.45(24)	-1.43(25)
C (12)	3.63(22)	3.08(22)	5.73(30)	-0.51(18)	1.23(20)	-0.34(20)
C (13)	3.94(22)	4.15(26)	3.02(21)	-0.69(19)	0.05(17)	-0.27(18)
C (14)	3.22(20)	4.15(25)	3.31(23)	-0.13(16)	0.33(17)	0.06(19)
C (15)	3.69(25)	4.27(27)	5.66(30)	0.31(20)	0.82(21)	-0.39(23)
C (16)	4.79(26)	4.23(28)	4.77(27)	0.55(22)	1.21(22)	-0.05(22)
C (17)	4.52(24)	3.53(23)	3.84(23)	0.39(19)	0.04(18)	-0.12(19)
C (18)	6.25(32)	7.06(40)	2.92(22)	-2.03(32)	0.38(21)	0.25(25)
C (19)	6.30(36)	6.01(38)	4.05(35)	-2.18(30)	2.53(29)	-2.78(30)
C (20)	4.77(26)	3.28(23)	4.35(24)	-0.03(20)	-0.09(20)	-0.29(19)
O (21)	5.70(21)	4.23(20)	6.34(24)	0.68(17)	0.78(18)	1.42(18)
C (22)	5.66(31)	4.39(35)	7.85(43)	-0.94(27)	-0.12(29)	1.28(32)
O (23)	5.75(22)	4.41(20)	6.39(24)	-1.31(17)	-0.16(18)	0.85(18)
C (24)	3.87(24)	4.07(28)	4.20(30)	-0.06(22)	-1.77(22)	-2.27(28)
O (25)	7.26(27)	4.90(25)	6.58(32)	-0.82(21)	2.66(24)	-2.10(25)
C (26)	3.05(21)	4.83(28)	4.77(27)	-0.49(20)	1.10(18)	-0.53(22)
C (27)	4.63(30)	8.48(51)	5.36(34)	-1.69(33)	1.50(26)	-1.22(34)
C (28)	6.39(33)	10.39(70)	4.90(32)	-2.68(42)	1.13(28)	1.28(39)
C (29)	4.70(30)	4.81(30)	4.30(30)	-0.39(25)	-0.05(26)	-2.27(30)
C (30)	5.67(31)	3.11(24)	6.43(34)	-0.67(25)	0.53(25)	-0.15(25)
C (31)	4.53(26)	3.73(25)	5.37(27)	-0.31(21)	1.36(22)	-0.10(22)
Br(32)	9.20(6)	8.01(6)	11.25(7)	-2.55(5)	-1.69(5)	4.84(6)
O (33)	6.93(25)	5.48(25)	5.18(21)	0.07(20)	2.44(18)	-0.66(18)
O (34)	5.79(20)	7.74(20)	4.20(16)	-0.11(15)	-0.19(14)	-0.42(14)
C (35)	3.23(20)	3.84(24)	4.44(25)	-0.22(16)	1.16(18)	-1.05(20)
F (36)	5.12(15)	5.37(18)	5.80(17)	-0.12(14)	2.62(15)	-0.71(14)
F (37)	4.91(14)	5.23(17)	4.09(14)	-0.25(13)	0.51(11)	-0.77(12)
O (38)	7.78(28)	5.93(26)	6.79(26)	-2.96(23)	4.25(23)	-2.31(22)
C (39)	5.02(34)	5.10(39)	3.50(23)	-0.11(23)	3.57(41)	-2.36(43)
N (40)	4.83(26)	3.01(26)	14.46(60)	0.19(19)	2.83(32)	-1.61(28)
N (41)	4.15(22)	3.36(21)	9.58(39)	0.15(16)	2.00(23)	-1.51(24)
C (42)	4.67(27)	3.27(24)	5.76(31)	0.56(21)	0.35(23)	0.16(22)
C (43)	6.42(35)	6.42(35)	7.66(29)	0.22(27)	1.39(26)	-0.55(25)
C (44)	7.04(43)	6.95(43)	5.06(32)	0.45(30)	2.06(30)	1.34(31)
C (45)	8.01(45)	4.90(35)	5.46(34)	-0.54(31)	1.44(30)	0.98(28)
C (46)	6.59(36)	5.51(35)	4.79(29)	-0.16(29)	0.36(25)	0.23(28)
C (47)	5.51(30)	3.68(26)	6.20(33)	0.30(24)	1.71(25)	-0.59(24)
C (48)	7.74(43)	6.94(43)	4.36(29)	-0.39(30)	1.19(28)	-1.10(30)
C (49)	15.03(77)	17.12(188)	23.60(212)	-2.18(168)	-4.81(179)	-3.27(170)
C (50)	14.19(84)	8.87(64)	3.66(31)	-0.72(57)	0.17(40)	0.75(36)
U (51)	6.76(26)	7.54(32)	5.78(23)	-2.10(24)	2.08(20)	-0.25(23)
C (52)	15.61(113)	10.84(105)	11.55(97)	-3.62(88)	3.53(86)	-2.52(80)
C (53)	20.79(226)	17.12(188)	23.60(212)	-2.18(168)	-4.81(179)	-3.27(170)
C (54)	16.59(111)	20.00(98)	13.35(85)	-0.34(72)	0.33(29)	2.48(169)
C (55)	27.91(144)	8.78(243)	20.19(168)	-0.34(172)	-5.94(123)	0.23(166)

several trials, the E map calculated from the refined phases rendered the gross features of the structure. A few atoms missing at this stage were located from subsequent Fourier syntheses based on phase angles determined from the atomic positions already found. Due to the rather large uncertainties in atomic positions determined from the E map, e.g. distances in the benzene rings varied between 1.10 to 1.90 Å, the positional parameters were first refined by four cycles of block-diagonal least-squares with isotropic temperature factors set at 4 Å<sup>2</sup>. At this stage anisotropic temperature factors were introduced and after seven more cycles the refinement was terminated. The last shifts were all well below the corresponding e.s.d.'s (6–20%) and the final R value was 0.06 for all 'observed reflections.

A difference Fourier synthesis calculated during the course of the refinement revealed that the atomic positions of the butanol molecule are poorly fixed. This is also manifested by the erratic distances found between atoms in this molecule. Except for the oxygen atom, the peaks are very wide and lower than normally expected. (Without including the butanol molecule in the calculations the R value converged at the value ~0.15.)

In the last three cycles the hydrogen atoms, except those on the methyl and hydroxyl groups, were included in the structure factor calculations with isotropic temperature factors of 4.5 Å<sup>2</sup>. The H positions were calculated from the C positions, assuming a C–H distance of 1.07 Å.

The absolute configuration of the molecule was not determined directly; rather we considered the configuration of naturally occurring steroids to be well established and used the geometry around C(13) when we assigned the configuration. However, considering the parameter errors possible in polar space groups when neglecting anomalous scattering (Cruickshank & McDonald, 1967, and references cited therein), both the real and the imaginary part of the anomalous dispersion correction for the Br atom were included in the least-squares calculation ( $Af''_{Br} = -0.96$  and  $Af'_{Br} = 1.46$ ).

The positional and thermal parameters for the final structure are given in Tables 1 and 2 respectively and the assumed hydrogen atom positions in Table 3. Observed and calculated structure factors are given in Table 4.

Table 3. Assumed hydrogen positions

	Hydrogen atoms at		
	X	Y	Z
C(1)	0.3772	-0.7784	0.5497
	0.3707	-0.7613	0.7283
C(4)	0.0640	-0.8928	0.7658
C(6)	-0.0413	-0.8105	0.6659
C(7)	-0.0755	-0.6502	0.5916
C(8)	0.0555	-0.6369	0.4877
C(9)	0.2342	-0.6774	0.7424
C(11)	0.3844	-0.6545	0.5994
C(12)	0.3583	-0.5236	0.5643
	0.3335	-0.5539	0.7307
C(14)	0.1261	-0.5811	0.7715
C(15)	-0.0683	-0.5390	0.7359
	-0.0596	-0.5105	0.5633
C(16)	-0.0028	-0.4030	0.6808
C(22)	0.3774	-0.4114	0.5751
	0.3795	-0.3681	0.7380
C(27)	0.3261	-0.2618	0.1607
C(28)	0.3544	-0.1464	0.0515
C(30)	0.4107	-0.0561	0.4691
C(31)	0.4018	-0.1766	0.5669
C(39)	0.4993	-0.9081	0.6173
C(43)	0.1379	-0.9739	0.9363
C(44)	0.0074	-1.0745	0.9801
C(45)	0.0138	-1.1861	0.8564
C(46)	0.1385	-1.2001	0.6686
C(47)	0.2526	-1.0996	0.6073

### The structure

Interatomic distances and angles calculated from the final positional parameters are given in Table 5 and are also shown in Fig. 1. Torsion angles and fold angles are given in Table 6. A projection of the structure along [001] is given in Fig. 2.

Table 4. Observed and calculated structure factors and phase angles. The columns are I, 10F<sub>o</sub>, 10F<sub>c</sub> and the phase angle.

Table with multiple columns containing numerical data for structure factors and phase angles, organized in rows and columns.

Table 4 (cont.)

A large table of numerical data with multiple columns and rows, containing various numbers and some text labels like 'M', 'K', 'L', 'S', 'T', 'U', 'V', 'W', 'X', 'Y', 'Z'.

Table 4 (cont.)

Atom 11, K1										Atom 12, K1										Atom 13, K1										Atom 14, K1									
11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	14	14	14	14	14	14	14	14	14	14
11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	13	13	13	13	13	13	13	13	13	13	14	14	14	14	14	14	14	14	14	14

Table 5. Interatomic distances

e.s.d.  $\times 1000$  are given in parentheses for identification of atoms compare with Fig. 1.

Atoms	Distances	Atoms	Distances
1-2	1.515 (11) Å	20-22	1.503 (10) Å
2-3	1.332 (10)	22-23	1.434 (10)
2-39	1.360 (11)	23-24	1.359 (9)
3-4	1.461 (9)	24-25	1.167 (9)
3-41	1.353 (8)	24-26	1.480 (10)
4-5	1.317 (9)	26-27	1.383 (10)
5-6	1.490 (8)	27-28	1.340 (16)
5-10	1.540 (9)	28-29	1.376 (14)
6-7	1.520 (8)	29-30	1.396 (11)
6-35	1.465 (8)	29-32	1.901 (7)
7-8	1.515 (8)	30-31	1.369 (10)
7-35	1.444 (8)	31-26	1.364 (9)
8-9	1.563 (8)	33-48	1.391 (10)
8-14	1.530 (8)	34-48	1.459 (9)
9-10	1.552 (9)	35-36	1.353 (7)
9-11	1.547 (8)	35-37	1.356 (7)
10-1	1.536 (9)	39-40	1.332 (11)
10-19	1.559 (10)	40-41	1.352 (9)
11-12	1.539 (9)	41-42	1.442 (9)
11-38	1.441 (9)	42-43	1.416 (10)
12-13	1.513 (8)	43-44	1.360 (12)
13-14	1.529 (8)	44-45	1.364 (12)
13-17	1.565 (8)	45-46	1.371 (12)
13-18	1.555 (8)	46-47	1.354 (11)
14-15	1.507 (8)	47-42	1.387 (10)
15-16	1.519 (9)	48-49	1.544 (15)
16-17	1.558 (9)	48-50	1.538 (13)
16-33	1.425 (8)	51-52	1.360 (10)
17-20	1.528 (9)	52-53	1.465 (20)
17-34	1.428 (7)	53-54	1.184 (37)
20-21	1.220 (8)	54-55	1.804 (41)

Inspection of Table 2 shows that while the majority of the  $B_{ii}$  are in the range commonly encountered, some values are rather large. In particular atoms 32, 39, 40, 49 and 50 show somewhat unusual behavior. The same is, to a greater extent, also true for atoms in the butanol molecule. While in the latter case this is undoubtedly due to disorder, it appears tempting to link the large  $B_{ii}$  values for atoms in the steroid molecule with deterioration of the crystal, indicated by the standard reflections. However, this aspect has not been investigated further.

The two compounds (I) and (II) differ only with respect to the substituents on the *D* ring, and one can expect corresponding bond lengths to have approximately the same values. The majority of corresponding bond lengths differ less than  $0.03 \text{ \AA}$  ( $\sim 3\sigma$ ), that is approximately  $1.5\sigma$  from the mean value. A few bond

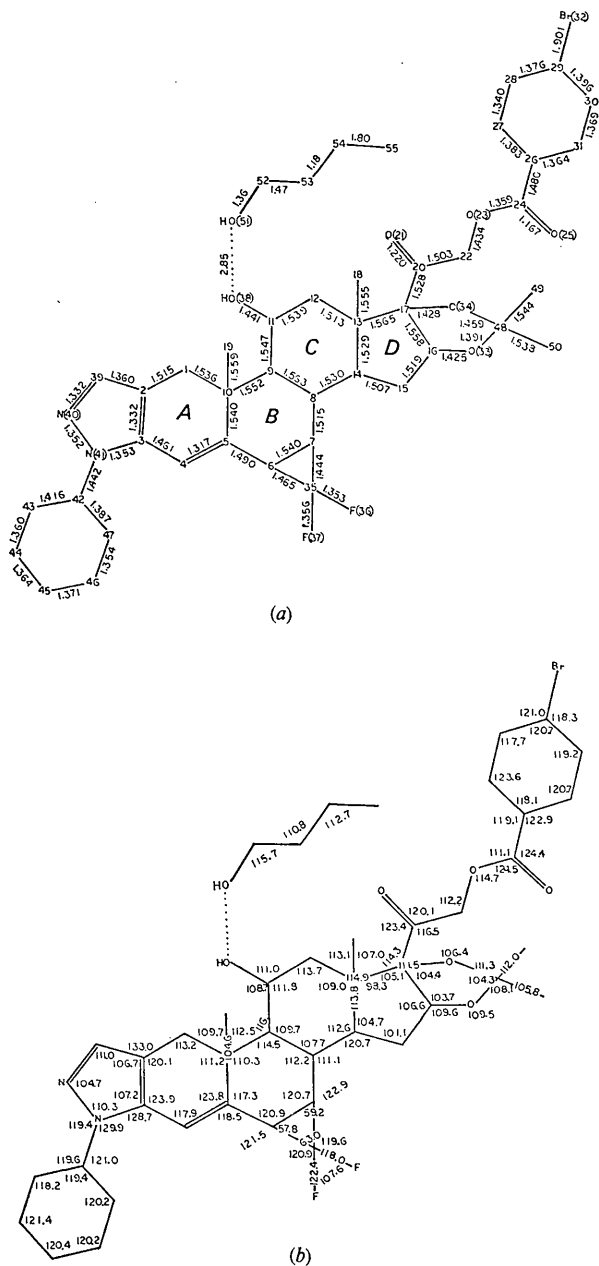
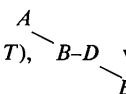



Fig. 1. (a) Bond lengths. (b) bond angles. The e.s.d.'s. are in the range  $0.4-0.8^\circ$  for angle in the steroid molecule and about  $2^\circ$  for angles in the butanol molecule.

Table 6. *Torsion and fold angles*

Torsion angle ( $T$ ),  view along  $B-D$ , angle is rotation of  $A-B$  to cover  $D-E$ , positive clockwise.

Fold angle ( $F$ ),  fold along  $D-B$ , angle is positive for  $B$  below  $ADE$  when viewed as in diagram.

$A$	$B$	$D$	$E$	angle	$A$	$B$	$D$	$E$	Angle
1	2	3	4	5.23 ( $T$ )°	13	14	8	9	62.13 ( $T$ )°
2	3	4	5	5.64 ( $T$ )	13	14	15	16	-46.26 ( $T$ )
2	3	41	40	-0.03 ( $T$ )	14	8	9	11	-58.40 ( $T$ )
3	41	40	39	1.61 ( $T$ )	14	15	16	17	24.39 ( $T$ )
3	4	5	10	7.33 ( $T$ )	15	16	17	13	4.70 ( $T$ )
4	5	10	1	-28.27 ( $T$ )	16	17	13	14	-31.14 ( $T$ )
5	6	7	8	2.34 ( $T$ )	17	13	14	15	48.28 ( $T$ )
5	6	35	36	-140.07 ( $T$ )	33	16	17	34	2.92 ( $T$ )
5	6	35	37	-4.31 ( $T$ )	39	2	3	41	-1.55 ( $T$ )
5	10	1	2	35.55 ( $T$ )	40	39	2	3	2.67 ( $T$ )
6	7	8	9	-18.66 ( $T$ )	41	40	39	2	-2.62 ( $T$ )
7	8	9	10	46.72 ( $T$ )	9	8	11	12	-49.04 ( $F$ )
8	7	35	36	142.74 ( $T$ )	9	8	11	14	-54.28 ( $F$ )
8	7	35	37	2.26 ( $T$ )	13	12	14	8	52.17 ( $F$ )
8	9	10	5	-57.12 ( $T$ )	13	12	14	11	46.79 ( $F$ )
8	9	11	12	54.40 ( $T$ )	15	17	14	13	47.97 ( $F$ )
9	10	5	6	39.12 ( $T$ )	15	16	17	33	-64.36 ( $F$ )
9	11	12	13	-52.55 ( $T$ )	15	16	17	34	-67.28 ( $F$ )
10	1	2	3	-26.82 ( $T$ )	16	17	14	13	32.01 ( $F$ )
11	12	13	14	52.77 ( $T$ )	35	7	6	5	-69.92 ( $F$ )
12	13	14	8	-58.78 ( $T$ )	35	7	6	8	-67.58 ( $F$ )

lengths, however, have rather different values:  $C(2)-C(3)$  and  $C(6)-C(7)$  were found to be 1.33 and 1.52 Å in (I), and 1.39 and 1.57 Å in (II), a difference of approximately  $3\sigma$  from their mean values.

The conformation of the  $A$  ring is puckered with  $C(1)$  and  $C(10)$  displaced in opposite directions (about 0.22 and 0.26 Å respectively) from the plane through the 2,4-diene system.

The  $B$  ring is in the half chair conformation with atoms  $C(9)$  and  $C(10)$  displaced 0.42 and 0.27 Å respectively from the least-squares plane through  $C(5)$ ,  $C(6)$ ,  $C(7)$  and  $C(8)$  (the corresponding displacements in (II) were 0.42 and 0.34 Å respectively). These atoms are coplanar to within 0.011 Å. The torsion angle  $C(5)-C(6)-C(7)-C(8)$  is approximately  $2^\circ$  and does not differ significantly from the value of about  $4^\circ$  found in (II). The fold angle between the above plane and the cyclopropane ring is approximately  $68^\circ$ .

In both (I) and (II) the distances  $C(35)-C(6)$  and  $C(35)-C(7)$  average 1.45 Å, and, as reported in the paper on (II), this is shorter than the value 1.51 Å reported by Bastiansen, Fritsch & Hedberg (1964) in the electron diffraction study of cyclopropane. The two  $C-F$  distances  $C(35)-F(36)$  and  $C(35)-F(37)$  average 1.375 Å in (II) and 1.355 Å in (I) and are in both compounds longer than the normal  $C-polyF$  bond length of 1.33 Å. This is consistent with contribution from the double bond—no bond resonance form illustrated in the paper on (II).

While the  $A$  and  $B$  ring moieties of (I) and (II) do not differ significantly, this is not the case for the  $C$

and  $D$  rings. In (II) the torsion angle  $C(14)-C(15)-C(16)-C(17)$  is  $5.5^\circ$ , indicating that the  $D$  ring is a slightly distorted  $\beta$  envelope, using the terminology of Brutcher & Leopold (1966). By introducing the  $16\alpha,17\alpha$ -isopropylidenedioxy group the  $D$  ring assumes the  $\alpha$ -envelope conformation, the torsion angle  $C(15)-C(16)-C(17)-C(13)$  is  $4.7^\circ$  and  $C(14)$  is displaced 0.70 Å from the least-squares plane through  $C(15)$ ,  $C(16)$ ,  $C(17)$  and  $C(13)$ .

The difference in  $D$  ring conformations causes a considerable change in the geometry of ring  $C$ . While the torsion angles in ring  $B$  in (I) and (II) do not differ significantly from their mean values, the torsion angle  $C(8)-C(9)-C(11)-C(12)$  is  $54.4^\circ$  in (I) and  $44.8^\circ$  in (II). For comparison of other corresponding torsion angles in the  $C$  rings see Table 8. Comparative least-squares calculations (Table 7) show that  $O(38)$  is displaced approximately 0.4 Å 'lower' in (II) than in (I). Distances from the least-squares plane through  $C(3)$ ,  $C(10)$ ,  $C(19)$ ,  $C(13)$  and  $C(18)$  in the two compounds are compared in Table 7, and the  $11\beta$ -hydroxyl group is about 0.34 Å closer to this plane in (I) than in (II). Another point of interest is the intramolecular distances  $C(18)-O(38)$  and  $C(17)-O(38)$  of 3.03 and 2.94 Å in (I) and 3.01 and 3.10 Å in (II) respectively. In view of the unique role the  $11\beta$ -hydroxyl group appears to play in corticoid activity, it is interesting to note the more equatorial (relative to the face of the steroid molecule) position of this group in (II) than in (I). The  $11\beta$ -hydroxyl group is thus less shielded in the more active compound.

Table 7. *Least-squares planes*

The normal equations are given. Deviations are in Å. Planes are defined by atoms listed before slash (/).

\* Denotes corresponding planes in (II).

- (1)  $2.7008X + 5.6933Y + 8.4706Z = 1.5404$ .  
Deviations: 2, 0.012; 3, -0.023; 4, 0.022; 5, -0.011/  
1, 0.223; 10, -0.258.
- (2)  $2.8782X + 4.8421Y + 8.5426Z = 2.2729$ .  
Deviations: 5, 0.005; 6, -0.011; 7, 0.010; 8, -0.005/  
9, 0.421; 10, -0.266.
- (3)  $-11.3982X - 2.2802Y + 0.5441Z = 2.0438$ .  
Deviations: 6, 0.000; 7, 0.000; 35, 0.000/ 36, 1.115;  
37, -1.069.
- (4)  $2.5350X - 9.2220Y + 7.7103Z = 9.8778$ .  
Deviations: 13, -0.0176; 15, 0.0183; 16,  
-0.028; 17, 0.0274/ 14, 0.699.
- (5)  $2.4713X + 3.9262Y + 8.7919Z = 3.2186$ .  
Deviations: 2, 0.004; 3, 0.062; 39, -0.013;  
40, -0.026; 41, 0.043; 42, -0.055; 4, 0.074; 5, -0.088/  
1, 0.066; 10, -0.451.
- (6)  $2.4374X + 4.5574Y + 8.7253Z = 2.6075$ .  
Deviations: 1, 0.126; 2, 0.0118; 3, 0.049; 4, 0.087;  
5, -0.030; 6, -0.004; 7, -0.005; 8, -0.084; 39, -0.040;  
40, -0.095; 41, -0.016/ 9, 0.304; 11, 0.179; 12, 0.997;  
38, -1.214.
- (6\*) Deviations: 1, 0.189; 2, 0.002; 3, 0.080; 4, 0.162; 5,  
0.001; 6, -0.084; 7, -0.056; 8, -0.055; 39, 0.141; 40,  
-0.109; 41, 0.009/ 9, 0.429; 11, 0.503; 12, 1.156; 38,  
-0.768.
- (7)  $-11.3017X - 0.8432Y + 3.2401Z = 0.2995$ .  
Deviations: 3, 0.010; 10, -0.026; 19, 0.014; 9, -0.007;  
13, 0.019; 18, -0.009/ 11, -1.290; 12, -1.227; 38,  
-1.477.
- (7\*) Deviations: 3, -0.037; 10, -0.012; 19, 0.057; 9, 0.014;  
13, 0.055; 18, -0.077/ 11, -1.308; 12, -1.188; 38,  
-1.823.

Table 8. *Torsion angles in ring C in (I) and (II)*

A	B	D	E	Angle (I)	Angle (II)
7	8	9	10	46.7°	49.9°
8	9	11	12	54.4	44.8
9	11	12	13	-52.5	-47.3
11	12	13	14	52.8	55.1
12	13	14	8	-58.8	-63.7
13	14	8	9	62.1	62.4

The majority of packing contacts are normal, the only short intermolecular distances being O(38)–O(51) and N(48)–O(51), 2.85 and 2.83 Å respectively. The distance 2.85 Å is somewhat longer than the O...O distance normally encountered for hydrogen bonds between oxygen atoms (2.50–2.80 Å, Pauling, 1960). However, considering that the position of O(51) appears to be better defined than the rest of the butanol molecule, it is possible that there is a weak hydrogen bond between the butanol molecule and the 11 $\beta$ -hydroxyl group.

In order to comment more fully on the parameters which are required for high biological activity, we are currently determining the crystal structure of a potent corticoid incorporating the 16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy group, but lacking the 6,7-difluoromethylene group.

The authors wish to thank Dr J. Fried of this institute for informative discussions.

#### References

- BASTIANSEN, O., FRITSCH, F. N. & HEDBERG, K. (1964). *Acta Cryst.* **17**, 538.
- BRENNER, S. A. & GUM, P. H. (1968). *The Tangent Formula Program for the X-ray Analysis of Noncentrosymmetric Crystals*. NRL Report 6697.

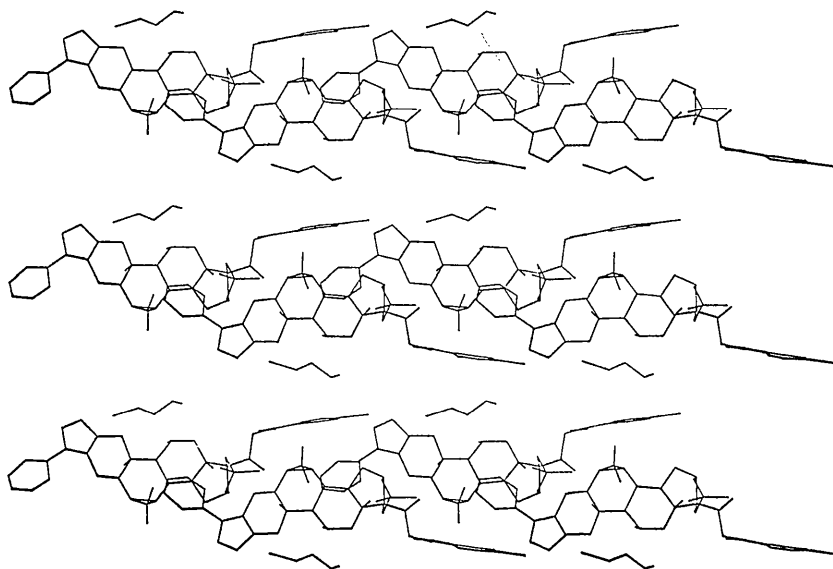


Fig 2. Projection of the structure along [001.] The *b* axis runs horizontally.



- BRUTCHER, F. V. & LEOPOLD, E. J. (1966). *J. Amer. Chem. Soc.* **88**, 3156.
- CHRISTENSEN, A. T. (1970). *Acta Cryst.* **B26**, 1519.
- CRUICKSHANK, D. W. J. & McDONALD, W. S. (1967). *Acta Cryst.* **23**, 9.
- HANSON, H. P., HERMAN, F., LEA, J. D. & SKILLMAN, S. (1964). *Acta Cryst.* **17**, 1040.
- HARRISON, I. T., BEARD, C., KIRKHAM, L., LEWIS, B., JAMIESON, I. M., ROOKS, W. & FRIED, J. H. (1968). *J. Medicinal Chem.* **11**, (4), 868.
- HOPE, H. & CHRISTENSEN, A. T. (1968). *Acta Cryst.* **B24**, 375.
- HUGHES, E. W. (1941). *J. Amer. Chem. Soc.* **63**, 1737.
- KARLE, J. & HAUPTMAN, H. (1956). *Acta Cryst.* **9**, 635.
- PATTERSON, A. L. (1935). *Z. Kristallogr.* **90**, 517.
- PAULING, L. (1960). *The Nature of the Chemical Bond*, p. 484. Ithica: Cornell Univ. Press.
- SIM, G. A. (1960). *Acta Cryst.* **13**, 511.
- SPARKS, R. A. (1961). In *Computing Methods and the Phase Problem in X-ray Crystal Analysis*. p. 170, paper 17. New York: Pergamon Press.

*Acta Cryst.* (1971). **B27**, 581

## The Crystal Structure of 2-Dimethylsulfuranylidene-1,3-indanedione\*

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(Received 18 March 1970)

2-Dimethylsulfuranylidene-1,3-indandione,  $C_{11}H_{10}SO_2$ , crystallizes in space group  $P2_12_12_1$ , with  $a = 18.331$ ,  $b = 9.012$ ,  $c = 5.949$  Å, estimated standard deviations 0.008 Å. The structure was refined by full-matrix, least-squares procedures to a final  $R$  value of 0.028. The refinement was based on 1170 reflections collected with an automatic diffractometer. The exocyclic C-S ylid bond distance is 1.71 Å, and confirms the view that there is an appreciable amount of double-bond character in this type of bond.

### Introduction

The recent interest in the chemistry of sulfonium ylids (Cook & Moffatt, 1968, and references cited therein) prompted the crystal-structure analysis of 2-dimethylsulfuranylidene-malononitrile (Christensen & Witmore, 1969), and the present work was carried out to continue the investigation of this class of compounds.

### Experimental

Crystals of 2-dimethylsulfuranylidene-1,3-indandione were kindly supplied to us by Dr John Moffatt. Preliminary precession photographs indicated orthorhombic symmetry. The systematic extinctions,  $h00$ ,  $0k0$  and  $00l$  with  $h$ ,  $k$  and  $l$  odd, are consistent with space group  $P2_12_12_1$ .

The crystal used for the determination of cell parameters and collection of intensity data was ground into a sphere of diameter 0.33 mm by the method of Bond (1951). The cell parameters and orientation parameters were refined by least-squares; the refinement gave the following results:  $a = 18.331$ ,  $b = 9.012$  and  $c = 5.949$  Å, with estimated standard deviations of the order 0.008 Å. These values give a calculated density of  $1.39 \text{ g.cm}^{-3}$  for  $Z = 4$ . The calculated linear absorption coefficient for copper radiation is  $25.8 \text{ cm}^{-1}$ . Inten-

sities were collected, using Ni-filtered  $\text{Cu } K\alpha$  radiation and an automated Picker diffractometer, of the 1200 reflections in the range  $0 < 2\theta < 160$  that were measured using the  $2\theta-\theta$  scan technique, 1170 had an intensity greater than three times the standard deviation and were recorded as 'observed'. No systematic change was detected in two standard reflections which were measured at regular intervals during the course of the data collection. The intensities were corrected for absorption using the spherical absorption factors published by Weber (1969).

### Determination and refinement of the structure

The position of the sulfur atom was determined from a sharpened Patterson function, and phase angles computed from the sulfur atom parameters were refined by the tangent formula (Karle & Hauptman, 1956). An  $E$  map calculated from the refined phases revealed the positions of all atoms other than hydrogen. The parameters of these atoms, anisotropic temperature factors included, were refined by full-matrix least squares. A difference Fourier synthesis calculated when the  $R$  index was 0.06 revealed the positions of the ten hydrogen atoms, but showed no other significant maxima or minima. Inclusion of the hydrogen atoms in the structure factor calculation changed  $R$  to 0.047. At this point it was apparent that the strong low-order reflections suffered from secondary extinction effects. After application of the correction method of Zachariasen (1963), reflections with  $\sin \theta/\lambda < 0.40 \text{ \AA}^{-1}$  were

\* Contribution No. 375 from the Syntex Institute of Organic Chemistry.

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