

## The Crystal and Molecular Structure of 12 $\alpha$ -Bromo-11 $\beta$ -hydroxyprogesterone

BY A. COOPER\* AND DORITA A. NORTON\*

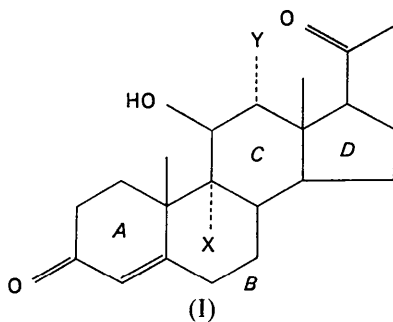
Center for Crystallographic Research, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14203, U.S.A.

(Received 4 August 1967)

The crystal and molecular structure of 12 $\alpha$ -bromo-11 $\beta$ -hydroxyprogesterone has been determined by X-ray diffraction techniques. The space group is  $P2_12_12_1$  with four molecules in a unit cell of dimensions  $a=7.902 \pm 0.001$ ,  $b=31.805 \pm 0.005$ ,  $c=7.577 \pm 0.002$  Å (at  $20 \pm 2^\circ\text{C}$ ). The structure was refined separately from two independent data sets to a final  $R$  value of 0.051 for 2256 reflections. The thermal motion of the molecules has been analysed, showing that the molecules have small librations about their long axes. Molecules pack in the unit cell in spirals, hydrogen bonded about the twofold screw axes parallel to  $a$ .

### Introduction

11 $\beta$ -Hydroxy-progesterone shows little, if any, progestational activity (Reichstein & Fuchs, 1940). By 9 $\alpha$ - or 12 $\alpha$ -halogenation [X and Y in (I)], however, activity over a wide range of hormonal and antihormonal effects is achieved, often surpassing progesterone in activity (Fried & Sabo, 1953; Hertz, Fried & Sabo, 1956). The almost equal activities of corresponding 9 $\alpha$ - and 12 $\alpha$ -halogenation products suggest that the enhancement in activity is a result of increase in acidity of the 11 $\beta$ -hydroxyl group, brought about by the inductive effect of the neighboring electrophilic  $\alpha$  substituent. The broad spectrum of activity of halogenated 11 $\beta$ -hydroxyprogesterone, such as is not normally found in a single steroid, prompted Fried (1957) to conclude that 'it is not unreasonable to assume that



11 $\beta$ -hydroxyprogesterone possesses in more or less embryonic form the spectrum of activities found in the halogenated derivatives. One might speculate then that the various individual sites of steroid action, be they corticoid or progestational, possess receptor surfaces attuned to the 11 $\beta$ -hydroxyprogesterone structure as the simplest common denominator. By creating different variants of the latter, such as oxygenation at positions 17, 18 and 21, or by omitting the 11 $\beta$ -hydroxyl

group, a mammalian organism is able to achieve specificity'.

The sample of 12 $\alpha$ -bromo-11 $\beta$ -hydroxyprogesterone used in this study was prepared by Squibb Laboratories and was supplied by the Cancer Chemotherapy Division of the National Institutes of Health. The steroid was recrystallized from methanol and unit-cell constants were measured on a General Electric Single Crystal Orienter. The space group was found to be orthorhombic,  $P2_12_12_1$  ( $h00$ ,  $0k0$  and  $00l$  absent for  $h$ ,  $k$  or  $l$  odd), and the unit-cell dimensions are  $a=7.902 \pm 0.001$ ,  $b=31.805 \pm 0.005$ ,  $c=7.577 \pm 0.002$  Å (at  $20 \pm 2^\circ\text{C}$ ; Cu  $K\alpha=1.5418$ ). The observed density (measured by flotation of the crystal in an aqueous solution of potassium iodide) is  $1.427 \text{ g.cm}^{-3}$  compared with a value of 1.428 calculated for four molecules of steroid ( $\text{C}_{21}\text{H}_{28}\text{O}_3\text{Br}$ ) per unit cell. The single-crystal melting point is  $232^\circ\text{C}$ .

### Determination of the structure

A uniform crystal was selected and ground into an approximately spherical shape with maximum dimension 0.25 mm. This crystal was mounted with its  $b$  axis parallel to the  $\varphi$ -axis of the diffractometer, and an indication of the anisotropy of absorption of X-rays by the crystal was obtained by examining the variation of diffracted X-ray intensity of the  $0k0$  spectra as  $\varphi$  was varied. This variation amounted to  $\pm 11$  per cent. The linear absorption coefficient ( $\mu$ ) for Cu  $K\alpha$  radiation is  $33.8 \text{ cm}^{-1}$ , and with  $\mu R=0.42$ , the maximum spherical absorption correction varies from approximately 1.8 at  $2\theta$  of  $0^\circ$  to 1.7 at  $150^\circ$ . This correction is effectively constant and may be combined with the overall scale factor for  $|F_o|$ , while the 11% shape anisotropy is sufficiently small so that the assumption of purely spherical shape is justifiable. The intensities of 2256 independent spectra with  $\sin \theta/\lambda$  less than 0.63 were measured on the single-crystal orienter using Cu  $K\alpha$  radiation. The stationary-crystal stationary-counter method was used and the intensity of each re-

\* Present address: Medical foundation of Buffalo, 73 High Street, Buffalo, New York 14203, U.S.A.

flexion was measured with a scintillation counter employing pulse height discrimination set to accept approximately 90% of the Cu  $K\alpha$  energy spectrum centered at 8 keV. Balanced nickel and cobalt filters were used to obtain the background-corrected intensities, an intensity measurement being made for a constant time of ten seconds with each filter for each reflection. Of the 2256 independent intensities which were measured, only 56 were classed as 'weak', with an observed intensity less than twice the standard deviation of the measurement. The usual Lorentz and polarization corrections were applied to the intensities, after which an absolute scale factor was obtained by Wilson's (1942) method; at the end of the refinement of the crystal structure, this scale factor had changed by only one per cent.

A three-dimensional Patterson synthesis was computed in which the  $|F_o|^2$  terms were multiplied by the expression  $\exp(3.6 \sin^2\theta)/f_{Br}^2$ , so that the Fourier coefficients were approximately those to be expected for point atoms at rest. The coordinates of the bromine atom were readily determined from the Harker sections, but no attempt was made to locate the other atoms from the Patterson synthesis, since experience with this space group indicates that the time spent in so doing is quite unrewarding as compared with the straightforward application of the heavy atom method to the phasing of Fourier coefficients. A set of structure factors calculated using the bromine atom alone produced an  $R$  value of 0.36, and from the three-dimensional Fourier synthesis calculated with these structure factors, 19 atomic positions were located. Two further successive structure factor and Fourier synthesis calculations employing the additional atoms obtained at each stage yielded all the 25 non-hydrogen atoms in the asymmetric unit (that is, in one steroid molecule). The positional and isotropic thermal par-

ameters of these atoms were refined by least-squares with a block-diagonal approximation to the normal equations ( $4 \times 4$  blocks for  $x$ ,  $y$ ,  $z$  and  $B$  of each atom), allotting weights inversely proportional to the variances of the observed structure amplitudes and using scattering factors obtained from *International Tables for X-ray Crystallography* (1962).<sup>\*</sup> Only the 56 'weak' reflections were removed from this refinement. After two cycles of refinement, anisotropic thermal parameters were introduced for the bromine atom and the weighting scheme was changed to

$$1/w = [(|F_o| - 15)/30]^2 + 1,$$

so that  $\langle w\Delta^2 \rangle$  was constant over the whole range of  $|F_o|$  values. This type of weighting scheme has been found to produce more rapid convergence of the iterative refinement process than does  $1/w = \sigma^2(|F_o|)$ . Another four cycles of refinement of all parameters gave  $R = 0.12$ . Anisotropic thermal parameters were now assigned to all atoms and after four cycles of refinement  $R$  had fallen to 0.072. A three-dimensional Fourier difference synthesis was now computed and this showed well-defined electron density at all the 29 expected hydrogen positions. These atoms were included in the least-squares refinement and all atoms were refined, keeping the isotropic thermal parameters of the hydrogen atoms fixed at  $2.0 \text{ \AA}^2$ . This was necessary, since it has been found that, owing to the uncertainty of the scattering factors for bonded hydrogen atoms, these thermal parameters usually become unreasonable when subjected to least-squares refinement. After three iterations  $R$  was reduced to 0.060.

Examination of the anisotropic thermal parameters of the heavier atoms after this refinement showed that

<sup>\*</sup> The bromine scattering factors were corrected for the real part of the anomalous dispersion correction for Cu  $K\alpha$  radiation:  $\Delta f' = -0.96$ .

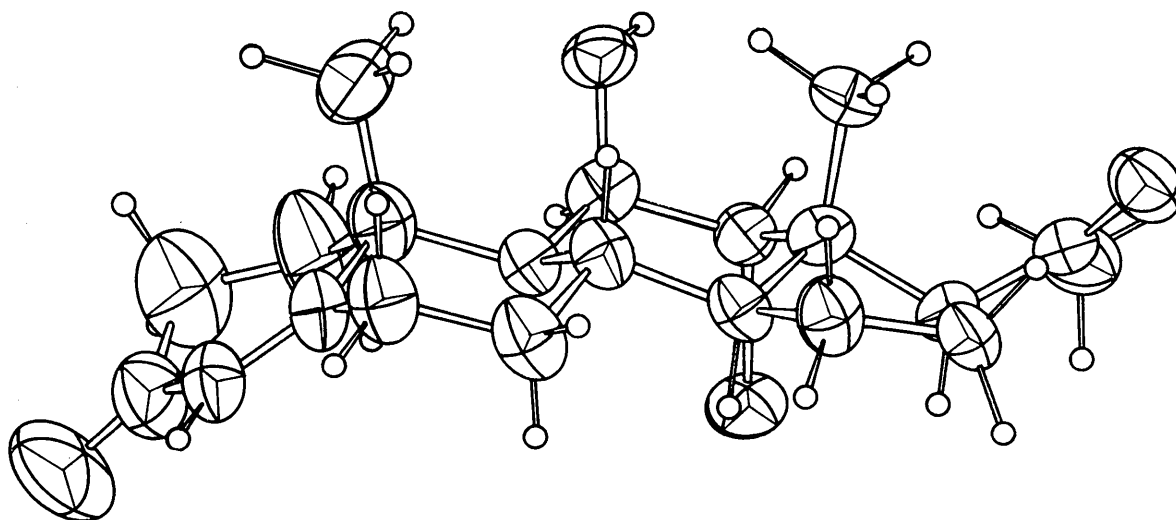


Fig. 1. The configuration of one steroid molecule, including the 50% probability thermal vibration ellipsoids of the non-hydrogen atoms.

atoms C(1), C(2), C(19) and O(3) appear to be vibrating much more strongly than the other atoms in the molecule. As our experimental techniques appeared to be able to produce extremely good data in terms of the final  $R$  value attainable, we felt that it would be worthwhile to rule out the possibility that some systematic error in the data collection was a contributing factor to these large vibrations, by remeasuring the intensity data with a different crystal.

A new batch of crystals was grown and a crystal of similar dimensions to that previously used was selected. This crystal was ground to a sphere and a new set of intensity data was collected. The final, refined parameters of the heavier atoms, as obtained above, but omitting atoms C(1), C(2), C(19) and O(3), were used to compute a three-dimensional Fourier difference synthesis, for which all the atoms were given isotropic thermal parameters of  $4.0 \text{ \AA}^2$ . The omitted atoms were located in this map and the various stages of the previous refinement were repeated, obtaining a final  $R$  value of 0.052.

The absolute configuration of the molecule was determined by computing a set of structure factors, including the imaginary part of the anomalous dispersion correction for the bromine scattering factors ( $\Delta f'' = 1.46$ ), firstly with the intensity data indexed as  $hkl$ , and secondly with them indexed as  $h\bar{k}l$ . In the first case, an  $R$  value of 0.051 was obtained, which, by applying Hamilton's (1965)  $R$  factor ratio test was found to be significantly better than the  $R$  value of 0.056 obtained in the second case (calculated with use of all reflections).

Refinement of the structure was terminated at this point with the minimization function  $\sum w\Delta^2/(m-n)$  at 0.999 and the calculated shifts less than one-third of a standard deviation. The agreement between the observed and calculated structure factors is summarized in Table 1; the full structure factor listing is given in Table 2. The standard deviations of the refined parameters were calculated from the inverses of the full normal equation blocks. The two sets of parameters are compared in Table 3, along with the  $t$  statistics calculated for the differences between the respective pairs of parameters ( $p_1$  and  $p_2$ ) for each of the  $j$  atoms, where

$$t = |p_1 - p_2|_j / (\sigma_1^2 + \sigma_2^2)^{1/2}.$$

Omitting for the moment the bromine atom parameters, ten parameter pairs out of a total of 216 (or 4.6%) are significant at the 5% level ( $t_{0.05} = 1.96$ ), a result which is in agreement with a random distribution of errors. For the bromine atom, the comparisons between  $U_{11}$ ,  $U_{22}$  and  $U_{33}$  are highly significant. This is not unexpected, however, since the mass absorption coefficient for bromine is comparatively high (100 for Cu  $K\alpha$  radiation, compared with 5 for carbon and 12 for oxygen) and, as was noted earlier, the crystals used were not perfectly spherical. Also, the parameter variances obtained from a block-diagonal least-squares

approximation tend to be underestimated, so that the  $t$  statistics would be somewhat overestimated. One is immediately encouraged by the striking similarity between the results of these two experiments: The average calculated standard deviations for set 2 are  $0.0059 \text{ \AA}$  and  $0.0067 \text{ \AA}^2$  for positional and thermal parameters, respectively, and these may be compared with corresponding values of  $0.0075 \text{ \AA}$  and  $0.0074 \text{ \AA}^2$  calculated from the variations between the parameters obtained from the two refinements. Thus, it would appear that the anomalies observed in ring  $A$  are not spurious. The configuration of the molecule is shown in Fig. 1. This figure includes the thermal vibration ellipsoids of the non-hydrogen atoms from which it is easy to see the effects of the high thermal parameters in the  $A$  ring.

Table 1. Summary of the agreement between the observed and calculated structure amplitudes at the end of the refinement of the second set of intensity data

(See text)

$ F_o $	Number of reflections	$\langle  F_o  \rangle$	$\langle  F_c  \rangle$	$\langle  \Delta  \rangle$	$R$
0.00– 4.99	415	3.40	3.08	0.81	0.239
5.00– 9.99	588	7.45	7.36	0.66	0.089
10.00– 14.99	410	12.24	12.57	0.73	0.059
15.00– 19.99	215	17.32	17.50	0.79	0.045
20.00– 29.99	279	24.48	24.62	0.84	0.034
30.00– 39.99	146	34.42	34.00	1.14	0.033
40.00– 49.99	78	44.39	43.49	1.23	0.028
50.00– 74.99	63	60.22	58.43	1.94	0.033
75.00– 99.99	16	85.93	84.32	2.41	0.028
100.00– 149.99	5	109.23	110.63	3.68	0.034
$\geq 150.00$	1	193.32	211.02	17.70	0.092

#### Analysis of the thermal motion of the atoms

Although conclusions drawn regarding thermal motion should be supported by additional data obtained at at least one lower temperature, the agreement between the two sets of thermal parameters, particularly between the sensitive  $U_{ij} (i \neq j)$  cross terms, suggested that an analysis of the thermal motion of the molecule would give meaningful results. Warnings regarding the analysis of vibrational effects extracted from unsubstantiated  $U_{ij}$  terms have been given by Lonsdale & Milledge (1961), so that we were pleased to find that our experimental techniques were capable of producing accurately reproducible results from different crystals of the same substance.

Using the observed  $U_{ij}$  terms obtained from the two structure analyses, one may calculate the tensors  $\mathbf{T}$  and  $\omega$  which describe the translational and librational motion of the molecules as a whole or of selected groups of atoms (Cruickshank, 1956a, b). By treating firstly the whole molecule as a rigid body, and secondly the whole molecule less atoms C(1), C(2), C(19) and O(3), it was clear that these last atoms are executing large out-of-plane, independent vibrations. If the molecule were behaving entirely as a rigid body, the  $\mathbf{T}$  and  $\omega$  tensors obtained for these two cases would be similar; in fact,

Table 2. Comparison of the observed structure amplitudes with those calculated from the refined parameters for this structure

The values are tabulated on ten times absolute scale and have been calculated for the second structure determination (see text).

Table with 16 columns (H, K, L, Fobs, Fcalc) and 16 rows of data. Each row represents a set of Miller indices (H, K, L) and compares observed (Fobs) and calculated (Fcalc) structure amplitudes. The data is organized in a grid-like format with multiple rows per set of indices.



Table 3. Comparison of the positional and anisotropic thermal parameters of the non-hydrogen atoms, as obtained from the two independent structure determinations

Standard deviations are given in parentheses. For each parameter listed, the figures give the result of the first structure determination, the result of the second structure determination and the  $t$  statistic for the difference between the two results. Thermal parameters are listed in the form

$$\exp - [2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \dots)]$$

	X/A	Y/B	Z/C	U11	U22	U33	U12	U13	U23
C 1	1.1830(25) 1.1824(11) 0.23	0.09617(48) 0.09622(23) 0.08	-0.2599(31) -0.2602(16) 0.08	0.0807(101) 0.0795( 48) 0.12	0.0613( 85) 0.0602( 41) 0.11	0.1475(187) 0.1624(103) 0.69	-0.0056( 78) -0.0091( 36) 0.41	0.0501(135) 0.0556( 69) 0.35	-0.0097(113) -0.0080( 56) 0.13
C 2	1.2968(25) 1.2940(11) 1.05	0.06598(63) 0.06553(31) 0.63	-0.3359(33) -0.3407(15) 1.33	0.0650(108) 0.0627( 45) 0.19	0.1253(131) 0.1165( 67) 0.59	0.1320(181) 0.1213( 78) 0.54	-0.0027(106) 0.0064( 48) 0.79	0.0181(134) 0.0157( 56) 0.16	-0.0004(135) 0.0038( 60) 0.28
C 3	1.2821(21) 1.2851( 9) 1.35	0.02455(55) 0.02504(24) 1.14	-0.2384(28) -0.2412(11) 0.94	0.0659( 68) 0.0624( 40) 0.36	0.0907(109) 0.0822( 46) 0.72	0.0822(134) 0.0806( 53) 0.11	0.0180( 64) 0.0144( 36) 0.38	0.0054(104) 0.0100( 43) 0.41	-0.0016(109) -0.0067( 41) 0.43
C 4	1.1177(19) 1.1184( 8) 0.36	0.01340(41) 0.01286(19) 1.19	-0.1924(22) -0.1835(10) 3.64	0.0736( 64) 0.0621( 37) 1.24	0.0483( 68) 0.0536( 31) 0.69	0.0761(101) 0.0710( 42) 0.46	0.0150( 63) 0.0147( 29) 0.05	0.0084( 81) 0.0088( 35) 0.04	-0.0043( 72) -0.0031( 32) 0.14
C 5	0.9837(17) 0.9858( 8) 1.09	0.03804(35) 0.03891(16) 2.27	-0.1836(20) -0.1785( 9) 2.40	0.0566( 72) 0.0536( 31) 0.36	0.0377( 54) 0.0357( 26) 0.33	0.0721( 86) 0.0618( 36) 1.11	0.0027( 53) 0.0028( 23) 0.01	0.0050( 68) 0.0101( 29) 0.68	-0.0054( 58) -0.0038( 24) 0.25
C 6	0.8167(20) 0.8161( 9) 0.25	0.02407(38) 0.02418(17) 0.25	-0.1239(25) -0.1148(11) 3.35	0.0712( 85) 0.0581( 36) 1.41	0.0345( 55) 0.0349( 26) 0.06	0.1068(125) 0.0970( 51) 0.72	-0.0049( 61) -0.0028( 27) 0.31	0.0249( 99) 0.0231( 41) 0.16	-0.0029( 72) -0.0030( 31) 0.00
C 7	0.7528(18) 0.7516( 8) 0.58	0.05233(35) 0.05200(16) 0.85	0.0422(22) 0.0362(10) 2.46	0.0641( 81) 0.0619( 36) 0.24	0.0301( 52) 0.0273( 21) 0.50	0.0993(103) 0.0839( 44) 1.37	-0.0056( 56) -0.0070( 25) 0.23	0.0150( 85) 0.0199( 37) 0.52	0.0055( 65) -0.0008( 27) 0.91
C 8	0.7494(15) 0.7495( 7) 0.08	0.09923(33) 0.09899(15) 0.64	-0.0165(17) -0.0153( 8) 0.66	0.0391( 60) 0.0353( 25) 0.58	0.0359( 51) 0.0315( 21) 0.80	0.0681( 70) 0.0579( 31) 1.31	-0.0032( 46) -0.0039( 20) 0.13	-0.0008( 60) 0.0017( 26) 0.39	-0.0011( 51) 0.0044( 23) 0.58
C 9	0.9257(16) 0.9231( 7) 1.51	0.11154(31) 0.11166(14) 0.35	-0.0842(16) -0.0838( 7) 0.22	0.0409( 58) 0.0383( 24) 0.41	0.0334( 49) 0.0306( 21) 0.52	0.0552( 63) 0.0544( 28) 0.11	0.0011( 50) -0.0023( 22) 0.63	0.0024( 64) 0.0009( 27) 0.22	0.0041( 47) 0.0043( 21) 0.03
C 10	0.9944(17) 0.9918( 8) 1.39	0.08437(34) 0.08426(16) 0.31	-0.2389(19) -0.2390( 9) 0.00	0.0620( 69) 0.0533( 29) 1.17	0.0408( 53) 0.0394( 35) 0.24	0.0578( 80) 0.0609( 35) 0.34	0.0011( 51) 0.0001( 22) 0.17	0.0149( 66) 0.0203( 29) 0.74	0.0012( 57) -0.0022( 26) 0.56
C 11	0.9305(17) 0.9404( 7) 0.49	0.15949(32) 0.15926(14) 0.67	-0.1143(15) -0.1172( 7) 1.73	0.0515( 65) 0.0476( 28) 0.55	0.0364( 50) 0.0320( 21) 0.82	0.0497( 60) 0.0441( 26) 0.84	-0.0074( 54) -0.0095( 23) 0.35	0.0203( 68) 0.0004( 29) 0.01	0.0032( 46) 0.0027( 20) 0.10
C 12	0.8813(14) 0.8816( 6) 0.16	0.18580(34) 0.18584(16) 0.11	0.0367(15) 0.0412( 6) 2.77	0.0489( 60) 0.0446( 26) 0.67	0.0394( 50) 0.0365( 21) 0.52	0.0433( 56) 0.0344( 22) 1.49	-0.0027( 50) -0.0085( 22) 1.04	-0.0083( 49) -0.0040( 20) 0.80	0.0018( 52) 0.0018( 22) 0.00
C 13	0.7101(14) 0.7121( 6) 1.31	0.17256(32) 0.17278(14) 0.62	0.1175(15) 0.1177( 7) 0.14	0.0405( 53) 0.0370( 24) 0.60	0.0425( 53) 0.0315( 21) 1.94	0.0449( 57) 0.0362( 24) 1.42	-0.0022( 45) -0.0000( 18) 0.44	0.0002( 51) -0.0024( 22) 0.47	0.0035( 46) 0.0036( 18) 0.01
C 14	0.7128(14) 0.7103( 6) 1.22	0.12529(32) 0.12492(14) 1.07	0.1481(17) 0.1479( 7) 0.06	0.0426( 56) 0.0386( 25) 0.65	0.0345( 49) 0.0318( 21) 0.51	0.0595( 68) 0.0477( 27) 1.60	-0.0017( 46) 0.0008( 20) 0.51	0.0041( 58) 0.0032( 24) 0.14	0.0060( 50) 0.0057( 21) 0.05
C 15	0.5475(16) 0.5461( 7) 0.86	0.11763(36) 0.11717(16) 1.17	0.2493(19) 0.2497( 8) 0.19	0.0504( 67) 0.0461( 29) 0.59	0.0528( 56) 0.0452( 29) 1.18	0.0669( 89) 0.0646( 37) 0.24	-0.0047( 53) -0.0046( 23) 0.01	0.0112( 74) 0.0125( 31) 0.16	0.0062( 61) 0.0076( 26) 0.20
C 16	0.5269(16) 0.5265( 7) 0.21	0.15650(36) 0.15704(17) 1.37	0.3698(18) 0.3673( 8) 1.24	0.0550( 73) 0.0478( 30) 0.91	0.0408( 57) 0.0434( 26) 0.40	0.0641( 72) 0.0537( 31) 1.33	0.0050( 54) 0.0047( 24) 0.04	0.0088( 65) 0.0088( 28) 0.00	0.0094( 55) 0.0105( 24) 0.18
C 17	0.6616(15) 0.6620( 6) 0.28	0.18814(34) 0.18821(15) 0.17	0.3052(15) 0.3048( 7) 0.22	0.0444( 59) 0.0437( 24) 0.11	0.0422( 52) 0.0391( 26) 0.54	0.0503( 58) 0.0358( 24) 2.32	0.0029( 50) 0.0043( 22) 0.25	-0.0053( 52) -0.0025( 22) 0.49	0.0100( 54) 0.0039( 23) 1.05
C 18	0.5725(16) 0.5723( 7) 0.13	0.18633(37) 0.18608(17) 0.60	-0.0100(16) -0.0116( 7) 0.91	0.0519( 60) 0.0483( 28) 0.54	0.0527( 59) 0.0472( 26) 0.86	0.0471( 63) 0.0471( 27) 0.00	0.0033( 64) 0.0051( 30) 0.25	-0.0084( 62) -0.0103( 27) 0.28	0.0037( 57) 0.0053( 25) 0.25
C 19	0.8881(31) 0.8875(12) 0.20	0.08799(47) 0.08731(20) 1.35	-0.4074(20) -0.4067( 9) 0.30	0.1544(201) 0.1258( 72) 1.35	0.0567( 79) 0.0512( 31) 0.65	0.0566( 77) 0.0542( 36) 0.27	0.0118(109) 0.0154( 41) 0.31	0.0107(117) 0.0148( 46) 0.32	-0.0071( 68) -0.0134( 30) 0.84
C 20	0.6092(16) 0.6110( 7) 1.06	0.23391(35) 0.23369(16) 0.57	0.3155(14) 0.3137( 7) 1.11	0.0571( 70) 0.0544( 31) 0.35	0.0417( 54) 0.0400( 26) 0.28	0.0397( 53) 0.0332( 25) 1.10	0.0059( 51) 0.0053( 22) 0.09	-0.0019( 53) -0.0043( 24) 0.42	0.0021( 46) 0.0027( 21) 0.10
C 21	0.7454(20) 0.7458( 9) 0.19	0.26663(38) 0.26694(19) 0.74	0.3133(23) 0.3071(12) 2.39	0.0646( 86) 0.0659( 38) 0.13	0.0474( 59) 0.0460( 31) 0.19	0.1042(107) 0.1014( 55) 0.23	0.0018( 62) 0.0025( 29) 0.10	-0.0248( 92) -0.0313( 44) 0.64	-0.0080( 73) -0.0103( 37) 0.28
O 3	1.4071(16) 1.4045( 7) 1.47	0.00346(51) 0.00190(24) 2.76	-0.2261(26) -0.2266(12) 0.17	0.0701( 78) 0.0673( 33) 0.32	0.1554(128) 0.1566( 62) 0.07	0.1520(151) 0.1567( 67) 0.28	0.0500( 87) 0.0547( 39) 0.50	0.0043(112) 0.0021( 48) 0.17	0.0185(130) 0.0073( 59) 0.79
O 11	0.8469(12) 0.8470( 5) 0.03	0.17168(23) 0.17146(10) 0.90	-0.2688(11) -0.2694( 5) 0.51	0.0777( 60) 0.0732( 25) 0.66	0.0375( 36) 0.0345( 15) 0.75	0.0429( 42) 0.0376( 18) 1.16	-0.0072( 39) -0.0044( 17) 0.67	-0.0017( 47) -0.0043( 20) 0.50	0.0035( 54) 0.0023( 35) 0.34
O 20	0.4621(12) 0.4627( 5) 0.42	0.24406(26) 0.24456(11) 1.80	0.3176(14) 0.3157( 6) 1.26	0.0622( 56) 0.0584( 24) 0.63	0.0460( 44) 0.0452( 21) 0.18	0.0898( 66) 0.0675( 26) 3.13	0.0154( 42) 0.0123( 18) 0.68	0.0037( 57) 0.0059( 23) 0.35	0.0100( 47) 0.0064( 20) 0.70
BR	1.0669( 2) 1.0668( 1) 0.34	0.18411( 5) 0.18415( 2) 0.70	0.2155( 2) 0.2157( 1) 0.95	0.0452( 6) 0.0420( 3) 5.05	0.0773( 8) 0.0730( 5) 4.65	0.0636( 7) 0.0555( 3) 10.74	-0.0082( 7) -0.0081( 3) 0.16	-0.0130( 7) -0.0139( 3) 1.12	-0.0048( 8) -0.0051( 3) 0.32

of the molecule. The coupling of motions of neighboring molecules and the presence of hydrogen bonding preclude large librations and, hence, the largest observed eigenvalue of  $\omega$  is only  $4.6^\circ$ .

If we subtract the rigid-body components from the observed  $U_{ij}$  terms for the non-rigid body atoms, we can obtain the independent motions of these atoms. These vibrations, which are shown in Fig.4 and in

Table 4(a). Comparison of  $\mathbf{T}$  and  $\omega$  calculated on the assumption that (a) all atoms and (b) all atoms except C(1), C(2), C(19) and O(3) vibrate as a rigid body

The estimated standard deviations are given in parentheses for the last two digits of each number. All values are referred to the molecule centered about its unweighted centroid. The results of the second structure determination were used in these calculations.

(a) All atoms

$$\mathbf{T} = \begin{bmatrix} 2.89 (46) & -0.54 (38) & -0.26 (41) \\ & 3.39 (41) & 0.89 (38) \\ & & 4.39 (48) \end{bmatrix} \times 10^{-2} \text{Å}^2$$

$$\omega = \begin{bmatrix} 7.1 (2.1) & -8.0 (1.9) & -4.3 (1.7) \\ & 22.6 (2.9) & 10.3 (2.0) \\ & & 14.0 (2.1) \end{bmatrix} \text{deg}^2$$

(b) All atoms except C(1), C(2), C(19) and O(3)

$$\mathbf{T} = \begin{bmatrix} 3.60 (21) & -0.37 (16) & -0.26 (18) \\ & 3.08 (17) & 0.69 (16) \\ & & 4.07 (21) \end{bmatrix} \times 10^{-2} \text{Å}^2$$

$$\omega = \begin{bmatrix} 10.5 (0.9) & -6.7 (0.9) & -4.4 (0.8) \\ & 10.8 (1.7) & 5.2 (1.1) \\ & & 8.9 (1.2) \end{bmatrix} \text{deg}^2$$

(a) and (b) are referred to the crystal axes  $a$ ,  $b$  and  $c$ .

(c) All atoms except C(1), C(2), C(19) and O(3) – referred to the principal axes of the rigid part of the steroid nucleus

$$\mathbf{T} = \begin{bmatrix} 4.44 & 0.10 & -0.39 \\ & 2.75 & 0.22 \\ & & 3.56 \end{bmatrix} \times 10^{-2} \text{Å}^2$$

$$\omega = \begin{bmatrix} 21.0 & -1.6 & 0.6 \\ & 3.9 & 0.0 \\ & & 5.3 \end{bmatrix} \text{deg}^2$$

Table 4(b). Principal axes of  $\mathbf{T}$  and  $\omega$

	Eigenvalues	Calculation (a)*				Eigenvalues	Calculation (b)*			
		Direction cosines of eigenvectors					Direction cosines of eigenvectors			
$\mathbf{T}$	0.050 Å	-0.233	0.521	0.822	0.046 Å	-0.382	0.460	0.801		
	0.032	-0.633	0.561	-0.535	0.035	-0.892	0.043	-0.450		
	0.025	-0.739	-0.644	0.199	0.027	-0.242	-0.887	0.394		
$\omega$	$33 (^\circ)^2$	-0.333	0.791	0.513	$21 (^\circ)^2$	-0.600	0.635	0.487		
	7	-0.209	0.469	-0.858	5	-0.554	0.110	-0.826		
	4	-0.919	-0.394	0.009	4	-0.578	-0.764	0.286		

\* Refers to the calculations in Table 4(a).

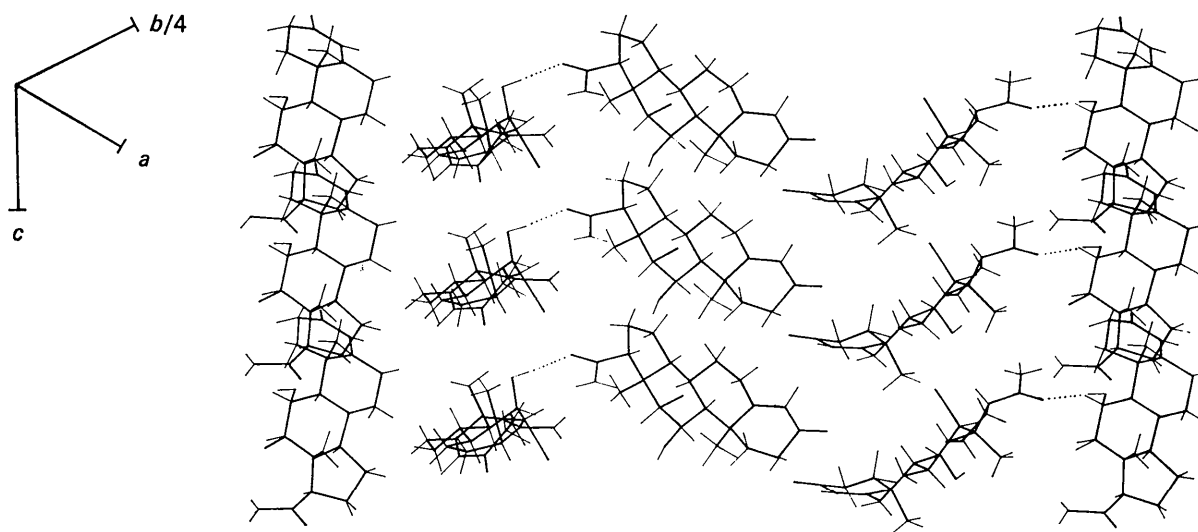


Fig. 3. Projection of several unit cells in the direction of the principal eigenvector of  $\omega$ . Reading from left to right, the molecules at the top of the Figure are  $(\frac{1}{2} - x, \bar{y}, z - \frac{1}{2})$ ,  $(x, y, z)$ ,  $(\frac{1}{2} + x, \frac{1}{2} - y, \bar{z})$ ,  $(3 - x, \frac{1}{2} + y, \frac{1}{2} - z)$  and  $(\frac{3}{2} - x, 1 - y, 1\frac{1}{2} + z)$ . The molecules are repeated down the page by unit cell translations in the  $c$  direction.

Table 5. *Non-rigid-body motions of atoms C(1), C(2), C(19) and O(3)*

The last two columns give the angles which the eigenvectors of  $\bar{u}_2$  and  $\bar{u}_3$  make with the least-squares plane through the atoms of the *A* ring.

	$(\bar{u}_1^2)^{1/2}$	$(\bar{u}_2^2)^{1/2}$	$(\bar{u}_3^2)^{1/2}$	$\varphi(\bar{u}_2)$	$\varphi(\bar{u}_3)$
C(1)	0.04 Å	0.15 Å	0.33 Å	2°	73°
C(2)	0.06	0.20	0.23	4	58
C(19)	0.04	0.10	0.25	10	-27
O(3)	0.04	0.25	0.27	-37	46

Table 5, are two-dimensional, the third principal axis of vibration in each case being effectively zero (less than two standard deviations).

With the exception of the *A* ring, all atoms in the molecule have van der Waals contacts with adjacent molecules; however, the closest approach of any atom to the *A* ring of an adjacent molecule is greater than the sum of the van der Waals radii of the atoms concerned, as may be seen by inspection of Table 9(b). Consequently, the *A* ring is quite free to vibrate at will. Atoms C(3) and C(4), being part of the resonance system involving the  $\Delta^4$  bond and the 3-keto group, do not take part in the non-rigid body motions. Atoms C(1), C(2) and O(3) are executing a seesaw type of motion with C(3) as the fulcrum. Since C(5) and C(9) are both components of inter-ring junctions, the  $sp^3$  orbitals of C(10), which are directed toward these two atoms, will resist distortion caused by the out-of-plane vibration of C(1). On the other hand, the two  $sp^3$  orbitals of C(10), which are directed toward C(1) and C(19), can be distorted in the plane of these three atoms so that vibration of C(1) can cause C(19) to reciprocate this motion.

#### Discussion of the structure

In Table 6 are listed the positional parameters of the atoms, averaged for the two structure determinations and corrected for libration of the molecule (Cruickshank, 1961) using a peak breadth parameter (Cruickshank's  $q^2$ ) of 0.1 Å<sup>2</sup> for all atoms, and rigid body parameters derived from the thermal motion of the respective atoms, averaged over the two structure determinations. Interatomic distances and angles calculated from these parameters are summarized in Fig. 5. The distances have standard deviations of 0.06 Å when they involve hydrogen atoms and are in the range 0.006–0.009 Å for heavier atoms. In the vicinity of C(1) and C(2) the standard deviations increase to 0.013 Å. Angles of the type H–C–H and H–C–C have standard deviations of 4° and 2°, respectively, while those involving only heavier atoms have standard deviations in the range 0.2–0.6°. For convenience, the interatomic distances are summarized below:

C–C distances	Expected	Observed
$sp^3$ – $sp^3$	1.533 (Bartell, 1959)	1.537 ± 0.010
$sp^3$ – $sp^2$	1.505 (Bartell & Bonham, 1960)	1.511 ± 0.008

$sp^2$ – $sp^2$	1.337 (Allen & Plyler, 1958)	1.338 ± 0.009
O=C=C=	1.44 (Sutton, 1965)	1.434 ± 0.010
C–O distances		
C=O	1.215 (Sutton, 1965)	1.213 ± 0.006
C–OH	1.426 (Sutton, 1965)	1.427 ± 0.007
C–H distances	1.01 (Jensen, 1962)	1.00 ± 0.06
O–H distances	0.88 (Ashida, Hirokawa & Okaya, 1965)	0.85 ± 0.06

With the exception of the bonds C(1)–C(2), C(1)–C(10), C(13)–C(17) and C(15)–C(16), all non-hydrogen bond distances are within two standard deviations of their expected values. The C–H distances show considerable variation, but little significance can be attached to individual differences. Jensen (1962) has remarked that C–H bonds, as determined by X-ray methods, may be shortened by as much as 0.03 Å. One is tempted to suggest that the strain produced by the fusion of rings *C* and *D* is responsible for the two long bonds in ring *D*. This strain, however, appears to have been transmitted throughout the whole molecule, as suggested by Robinson & Whalley (1963), so that little strain remains concentrated in the region of the *D* ring. Hendrickson (1961) has calculated the conformations of cyclopentane in various states of minimum energy, by varying the interatomic angles independently about the tetrahedral value, until a conformation of minimum energy was found for a given tor-

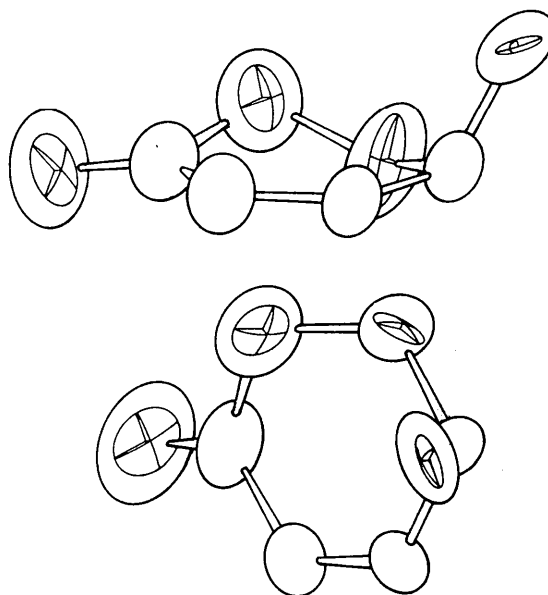


Fig. 4. Comparison of the rigid body and independent motions of the atoms in ring *A*. The outer ellipses are the envelopes corresponding to the observed thermal parameters. Inside each is drawn the ellipsoid representing the vibrations after subtraction of the rigid body motion. (These differences are not drawn for atoms C(3), C(4), C(5) and C(10), since, in these cases, the differences were not significantly different from the observed standard deviations.)



Table 6. *Positional parameters for the correct absolute configuration of the molecule*

These parameters have been corrected for libration of the molecule and have been averaged for the two structure determinations.

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
C(1)	1.1822	0.0961	-0.2639
C(2)	1.2940	0.0657	-0.3397
C(3)	1.2852	0.0249	-0.2399
C(4)	1.1190	0.0128	-0.1832
C(5)	0.9854	0.0386	-0.1786
C(6)	0.8152	0.0239	-0.1152
C(7)	0.7511	0.0518	0.0359
C(8)	0.7493	0.0989	-0.0149
C(9)	0.9245	0.1116	-0.0835
C(10)	0.9925	0.0841	-0.2393
C(11)	0.9405	0.1595	-0.1172
C(12)	0.8822	0.1859	0.0406
C(13)	0.7119	0.1730	0.1178
C(14)	0.7112	0.1250	0.1488
C(15)	0.5452	0.1171	0.2500
C(16)	0.5262	0.1568	0.3682
C(17)	0.6621	0.1883	0.3059
C(18)	0.5714	0.1865	-0.0115
C(19)	0.8889	0.0875	-0.4089
C(20)	0.6106	0.2341	0.3145
C(21)	0.7467	0.2673	0.3099
O(3)	1.4059	0.0018	-0.2265
O(11)	0.8476	0.1716	-0.2704
O(20)	0.4626	0.2448	0.3160
Br	1.0697	0.1843	0.2163

Table 6 (cont.)

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
H(1A)	1.2013	0.1087	-0.1168
H(1B)	1.1534	0.1240	-0.3504
H(2A)	1.4007	0.0784	-0.2672
H(2B)	1.2299	0.0700	-0.4405
H(4)	1.1005	-0.0142	-0.1040
H(6A)	0.8174	-0.0076	-0.1756
H(6B)	0.7308	0.0280	-0.1757
H(7A)	0.6233	0.0429	0.0562
H(7B)	0.8079	0.0500	0.1455
H(8)	0.6486	0.1056	-0.0916
H(9)	0.9964	0.1068	0.0025
H(11)	1.0593	0.1642	-0.1386
OH(11)	0.8955	0.1953	-0.2785
H(12)	0.8871	0.2170	0.0049
H(14)	0.7926	0.1228	0.2373
H(15A)	0.5301	0.0894	0.3285
H(15B)	0.4522	0.1165	0.1768
H(16A)	0.5374	0.1445	0.4764
H(16B)	0.4140	0.1649	0.3423
H(17)	0.7403	0.1851	0.3705
H(18A)	0.5775	0.2050	-0.0331
H(18B)	0.4602	0.1795	0.0608
H(18C)	0.5825	0.1713	-0.1268
H(19A)	0.9157	0.1183	-0.4712
H(19B)	0.7429	0.0870	-0.3771
H(19C)	0.9518	0.0653	-0.5080
H(21A)	0.7033	0.2947	0.3184
H(21B)	0.7737	0.2723	0.3740
H(21C)	0.8379	0.2582	0.3080

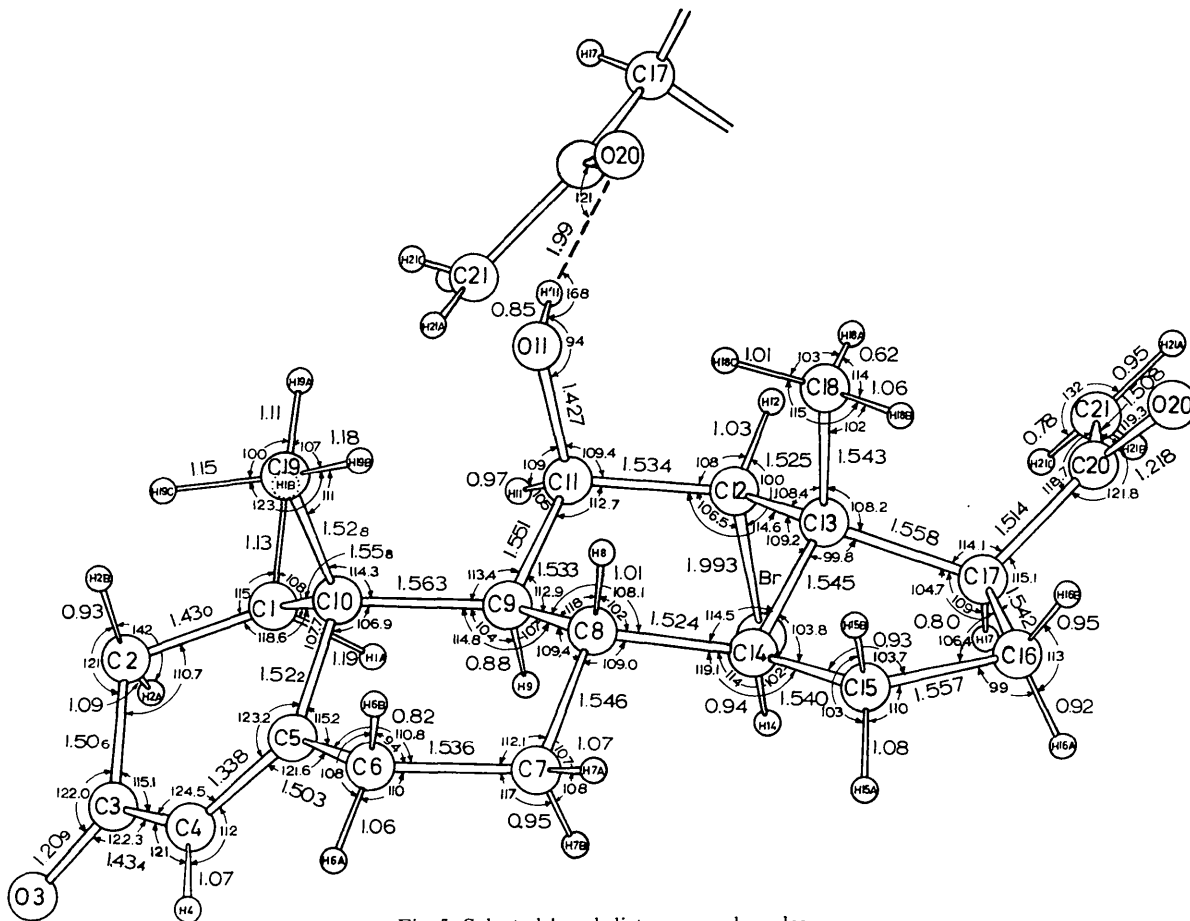


Fig. 5. Selected bond distances and angles.

sional angle. His calculated interatomic angles and torsional angle for  $\phi(13-17) = -40.0^\circ$  are compared in Fig. 6 with the corresponding values found in this steroid.

The geometry of C(2) in ring *A* is uncertain because of the high thermal motion of atoms C(1) and C(2). The approximate correction for these bond lengths to compensate for the non-rigid body motion of these atoms is calculated to lie in the range 0.001–0.412 Å (Busing & Levy, 1964).

As yet, insufficient evidence has accumulated regarding the expected values of interatomic angles in steroids. These angles are usually larger than the normal tetrahedral angle, owing to the flattening of the cyclohexane rings, and, since they are more sensitive to the effects of strain than are interatomic distances, comparatively large variations are usually observed. The angles in ring *D* have already been mentioned and those in rings *B* and *C* are in accord with angles found in other steroids (Norton, 1965). In ring *A*, the angle C(10)–C(1)–C(2) of  $118.6^\circ$  is very much larger than is expected for tetrahedral carbon atom. Apart from fac-

tors due to the thermal motion of atoms C(1) and C(2), this angle might be expected to be enlarged in order to relieve the strain introduced in the ring by the unsaturated C(4)=C(5) bond, and such enlargement has been observed in other steroids with  $\Delta^4$  bonds in the *A* ring [ $115^\circ$  in testosterone (Cooper, Gopalakrishna & Norton, 1968);  $114^\circ$  in 9-bromo-17 $\beta$ -hydroxy-17 $\alpha$ -

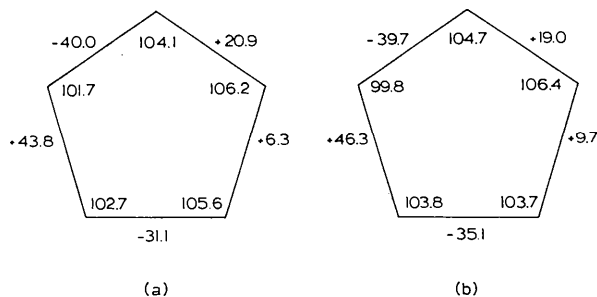


Fig. 6. Comparison of the torsional and interatomic angles calculated by Hendrickson (1961) for a free cyclopentane ring (a) with those observed in this structure (b).

Table 7(a). Least-squares planes through the atoms

The planes are of the form  $lX + mY + nZ = p$ , where  $X$ ,  $Y$ ,  $Z$  and  $p$  are in Å relative to the crystal axes.

Plane	Atoms	<i>l</i>	<i>m</i>	<i>n</i>	<i>p</i>
A1	C(2), C(3), C(4)	0.1369	0.4925	0.8595	0.217
A2	C(1), C(2), C(4), C(5)	0.4111	0.1266	0.9028	2.283
A3B1	C(1), C(5), C(6), C(10)	0.1170	0.3120	0.9429	0.097
B2	C(6), C(7), C(9), C(10)	0.7731	-0.2879	0.5652	4.268
B3C1	C(7), C(8), C(9), C(11)	0.2916	0.1907	0.9374	2.258
C2	C(8), C(11), C(12), C(14)	0.7818	-0.3729	0.5000	3.436
C3D1	C(12), C(13), C(14), C(15)	0.4218	0.1285	0.8946	3.969
D2	C(13), C(15), C(16), C(17)	0.7854	-0.3918	0.4792	2.761
D3	C(14), C(15), C(16), C(17)	0.5719	-0.3623	0.7360	2.566
A	C(1), C(2), C(3), C(4), C(5), C(10)	0.2873	0.2444	0.9262	1.322
B	C(5), C(6), C(7), C(8), C(9), C(10)	0.6465	-0.1004	0.7563	3.656
C	C(8), C(9), C(11), C(12), C(13), C(14)	0.6708	-0.2037	0.7131	3.506
D	C(13), C(14), C(15), C(16), C(17)	0.7306	-0.2709	0.6268	3.466
C(1)–C(17)		0.5929	-0.1279	0.7951	3.565
C(5)–C(17)		0.6988	-0.1733	0.6941	3.899

Table 7(b). Deviations (Å) from the least-squares planes

	A	B	C	D	A2	A3B1	B2	B3C1	C2	C3D1	D2	D3	C(1)–C(17)
C(1)	0.26				0.14	0.06							-0.01
C(2)	-0.26				-0.14								0.18
C(3)	0.10				0.35								0.91
C(4)	0.03				0.15								0.52
C(5)	-0.04	0.23			-0.15	-0.08	0.63						-0.18
C(6)		-0.23				0.07	0.00						-0.54
C(7)		0.22					0.00	0.04					-0.04
C(8)		-0.23	-0.26				-0.66	-0.04	-0.04				-0.55
C(9)		0.23	0.22				0.00	-0.05	0.63				-0.19
C(10)	-0.09	-0.23			-0.36	-0.05	0.00						-0.70
C(11)			-0.19					0.04	0.04				-0.51
C(12)			0.18						-0.04	0.05			0.06
C(13)			-0.22	-0.27					-0.64	-0.06	-0.07	-0.69	-0.22
C(14)			0.26	0.27					0.04	-0.04	0.64	0.04	0.16
C(15)				-0.14						0.05	0.07	-0.06	0.02
C(16)				-0.03							-0.11	0.06	0.48
C(17)				0.19							0.11	-0.04	0.61

Table 7(c). *Interplanar angles*

Plane 1	Plane 2	Angle
A1	A2	153.5°
A3B1	A2	159.9
A3B1	B2	122.3
B3C1	B2	134.5
B3C1	C2	128.7
C3D1	C2	137.2
C3D1	D2	135.6
C3D1	D3	148.9
A	B	149.5
B	C	173.4
C	D	172.9
[C(1)–C(17)]	(100)	126.4
[C(1)–C(17)]	(010)	82.7
[C(1)–C(17)]	(001)	142.7

methylandro-4-ene-3,11-dione (Cooper, unpublished).

The major least-squares planes which describe the steroid nucleus are given in Table 7(a), along with departures of the atoms from these planes [Table 7(b)] and interplanar dihedral angles [Table 7(c)]. Of interest here is the severe flattening of rings B and C, with dihedral angles at the ring junctions which are up to 20° from those to be found in the free (chair-shaped) cyclohexane ring (*cf.* Fig. 7). This flattening is quite usual in steroids (Norton, 1965) and is due to the transmission of strain effects through the molecule. In ring C, we have an additional effect supplementing the flattening. The 11 $\beta$ -hydroxyl group is strongly influenced by the proximity of the C(18) and C(19) methyl groups, so that it is forced outward, flattening the ring at the C(11)–C(12) bond. The torsional angles about this bond are shown in Fig. 8, where it may be seen that  $\varphi(\text{HO}-11-12-9)$  has been increased by 16°, with

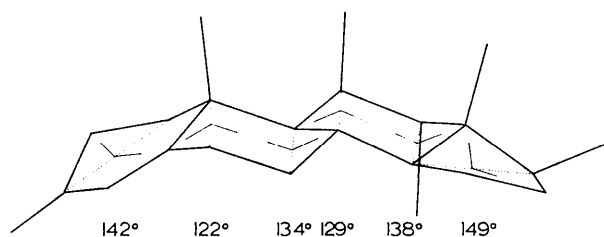


Fig. 7. Some dihedral angles in the steroid nucleus.

Table 8. *Torsional angles in the rings*

$\varphi_{A-B}$  is the torsional angle about the A–B bond, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question.

A ring		B ring		C ring		D ring	
Bond	$\varphi_{A-B}^*$	Bond	$\varphi_{A-B}$	Bond	$\varphi_{A-B}$	Bond	$\varphi_{A-B}$
C(1)–C(2)	–53.9°	C(5)–C(6)	–56.8°	C(9)–C(11)	+50.4°	C(13)–C(14)	+46.3°
C(2)–C(3)	+39.4	C(6)–C(7)	+54.3	C(11)–C(12)	–48.0	C(14)–C(15)	–35.1
C(3)–C(4)	–15.2	C(7)–C(8)	–53.2	C(12)–C(13)	+49.4	C(15)–C(16)	+9.7
C(4)–C(5)	+2.0	C(8)–C(9)	+54.7	C(13)–C(14)	–56.4	C(16)–C(17)	+19.0
C(5)–C(10)	–12.1	C(9)–C(10)	–54.1	C(14)–C(8)	+59.1	C(17)–C(13)	–39.7
C(10)–C(1)	+39.6	C(10)–C(5)	+54.7	C(8)–C(9)	–54.7		

\* The sign convention for the direction of the torsional angle is that of Klyne & Prelog (1960).

a concomitant decrease of  $\varphi(9-11-12-13)$  by 11°. Examination of Table 9(a) shows that, even with this distortion, H(18C) and H(19A) are still exerting strong steric forces on O(11). The flattening of the other rings may be seen from the list of torsional angles given in Table 8.

Table 9(a). *Important intramolecular contacts involving hydrogen atoms*

Contact	Distance	Contact	Distance
H(18A)–O(11)	2.99 Å	H(19B)–O(11)	2.94 Å
H(18B)–H(15B)	2.19	H(19B)–H'(11)	2.18
H(18B)–H(16B)	2.20	H(19B)–H(6B)	2.43
H(18C)–O(11)	2.36	H(19C)–H(1B)	2.74
H(18C)–H'(11)	2.84	H(19C)–H(2B)	2.27
H(18C)–H(8)	2.37	H(21A)–O(20)	2.49
H(19A)–O(11)	2.35	H(21B)–O(20)	2.66
H(19A)–H'(11)	2.86	H(21C)–H(12)	2.68
H(19A)–H(1B)	2.10	H(16B)–O(20)	2.58

Table 9(b). *Intermolecular contacts involving hydrogen atoms (less than 3.0 Å)*

The atoms marked with an asterisk are on the  $\alpha$  side of the molecule.

Equivalent position nomenclature: the symbol 3/1 $\bar{1}$ 0 is taken to mean that the second atom mentioned in the contact is in the molecule at equivalent position 3, translated 1, –1, and 0 unit cells in the a, b and c directions respectively. The equivalent positions are 1 = (x, y, z); 2 = ( $\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$ ); 3 = ( $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$ ).

Contact	Position	Distance
*H(1A)–H(15B)	1/100	2.98 Å
H(1B)–H(21A)	1/ $\bar{1}$ 0 $\bar{1}$	2.62
H(2A)–H(19B)	1/100	2.83
H(2A)–H(8)	1/100	2.51
H(2B)–H(15A)	1/10 $\bar{1}$	3.00
H(4)–H(15A)	3/1 $\bar{1}$ $\bar{1}$	2.63
H(6A)–H(19B)	3/1 $\bar{1}$ 0	2.96
H(6A)–H(19C)	3/1 $\bar{1}$ 0	2.84
H(6A)–H(7B)	3/1 $\bar{1}$ 0	2.68
H(6A)–H(15B)	3/1 $\bar{1}$ 0	2.94
H(6B)–H(7B)	3/1 $\bar{1}$ $\bar{1}$	2.83
*H(7B)–H(19C)	1/00 $\bar{1}$	2.89
H(11)–H(21A)	2/00 $\bar{1}$	2.19
H'(11)–H(17)	1/00 $\bar{1}$	2.94
H'(11)–C(20)	2/00 $\bar{1}$	2.83
H'(11)–O(20)	2/00 $\bar{1}$	1.99
H'(11)–H(21A)	2/00 $\bar{1}$	2.47
H(12)–O(20)	2/00 $\bar{1}$	2.78
H(12)–H(18A)	2/00 $\bar{1}$	2.90

Table 9(b) (cont.)

Contact	Position	Distance
*H(14)—C(19)	1/001	3.00
*H(14)—H(19A)	1/001	2.40
*H(14)—H(19C)	1/001	2.93
H(15A)—H(19B)	1/001	2.79
*H(16A)—H(19B)	1/001	2.68
H(16B)—*Br	1/T00	2.95
*H(17)—H(19A)	1/001	2.80
H(21A)—C(11)	2/T0T	2.96
H(21B)—O(20)	2/000	2.83

Table 9(c). Intermolecular distances between non-hydrogen atoms (less than 4.0 Å)

Contact	Position	Distance
C(6)—O(3)	1/T00	3.416 Å
C(6)—C(7)	3/1TT	3.613
C(7)—O(3)	1/T00	3.733
C(11)—C(20)	2/00T	3.936
C(11)—C(21)	2/00T	3.662
C(11)—O(20)	2/00T	3.401
C(12)—O(20)	2/00T	3.545
C(14)—C(19)	1/001	3.824
C(15)—C(19)	1/001	3.865
C(16)—Br	1/T00	3.886
C(16)—C(19)	1/001	3.991
C(16)—O(11)	1/001	3.764
C(17)—O(11)	1/001	3.569
C(18)—C(21)	2/T0T	3.722
C(20)—O(11)	2/T0T	3.664
C(21)—O(20)	2/000	3.331
C(21)—O(11)	2/T0T	3.717
O(11)—O(20)	2/00T	2.831
O(20)—Br	1/T00	3.730

Fig. 9 is a view of the molecule projected parallel to the least-squares plane through atoms C(5) to C(17), showing the striking deviation of ring *A* from the plane of the remainder of the molecule. If the atoms O(3)=C(3), C(2)—C(4)=C(5)—C(6), C(10) were truly planar,

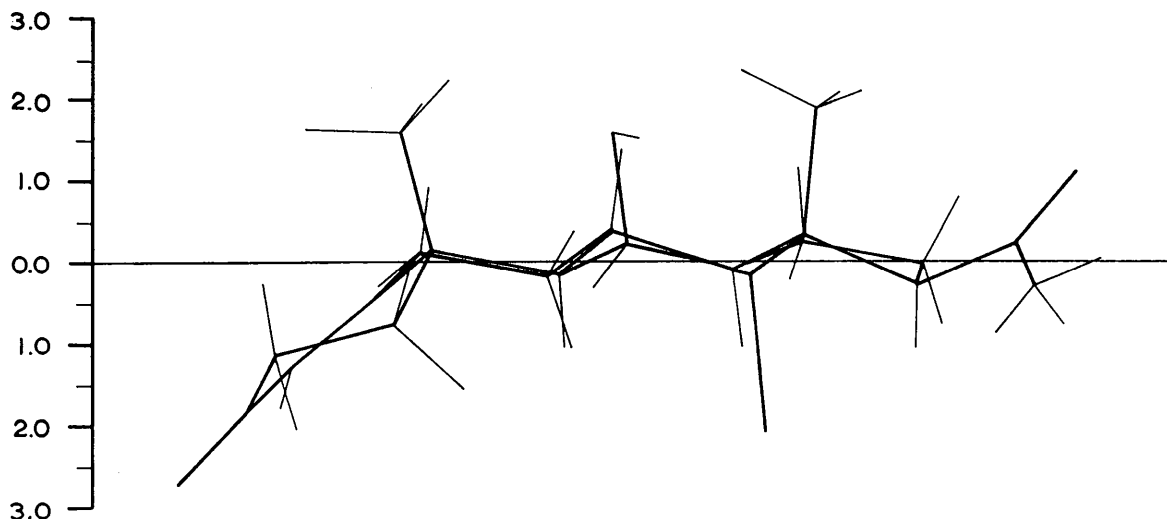


Fig. 9. Projection of the molecule parallel to the least-squares plane through atoms C(5) to C(17). The scale is in Å.

ar, as expected for a conjugated system, ring *A* would continue in the line of the molecule, but in the present case, although atoms C(3), C(4), C(5), C(6) and C(10) are planar with an r.m.s. deviation from their plane of 0.006 Å, atom O(3) is 0.12 Å out of the plane, changing the torsional angle  $\varphi(3-4)$  from the expected value of 0° to -15°. This has the effect of positioning atoms C(1) and C(2), 0.28 and 0.31 Å, respectively, on either side of the 'conjugation plane'.

At the other end of the molecule, ring *D* has a distorted  $\beta$ -envelope configuration, and the plane of atoms C(17), C(20), C(21) and O(20) lies at 41° to the planar part of ring *D* (plane *D3* in Table 7). In a single steroid molecule, the acetyl group at C(17) is free to rotate about the C(17)—C(20) bond by almost 180°, encountering steric hindrance by H(16B), H(18A) and H(18B). Owing to the formation of hydrogen bonding involving O(20), however, the stereochemistry of the acetyl group is uniquely defined with  $\varphi(13-17-20-21)$  of -79°.

### Packing of the molecules

Those molecules which are related by the screw axis parallel to *a* are hydrogen bonded *via* the 11 $\beta$ -hydroxyl and the 20-keto groups. Each spiral of molecules so formed is surrounded by six similar spirals, so that

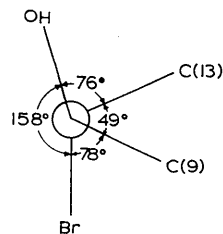


Fig. 8. Conformation of the bromine atom and the hydroxyl group about the C(11)—C(12) bond.

they are closest packed, as may be seen quite clearly in the (100) projection [Fig. 10(a)]. As was pointed out earlier, there are intermolecular van der Waals contacts along both surfaces of the molecule except for ring *A*. Owing to the irregularity caused by the bromine atom, however, the number of contacts on the  $\alpha$ -surface has been reduced to eight, compared with 20 to the  $\beta$ -surface [Table 9(b)]. Except for the atoms involved in the hydrogen bonding, all intermolecular distances are greater than the sums of the van der Waals radii for the various atoms. The closest contacts are,

as might be expected, to those atoms in the vicinity of the hydrogen bond. Inspection of the (001) projection [Fig. 10(b)] shows the manner in which the ketone oxygen atom O(20) fits neatly into the space adjacent to the hydroxyl group, with intermolecular contacts to H(12) and to the C(21) methyl group, so determining the geometry of the hydrogen bond, as shown in Fig. 5. The hydrogen bond is a little longer than the average value of  $2.72 \pm 0.04$  Å given by Wallwork (1962) and the angle of  $168 \pm 6^\circ$  between atoms O-H...O is within two standard deviations of being linear. Atom H(11')

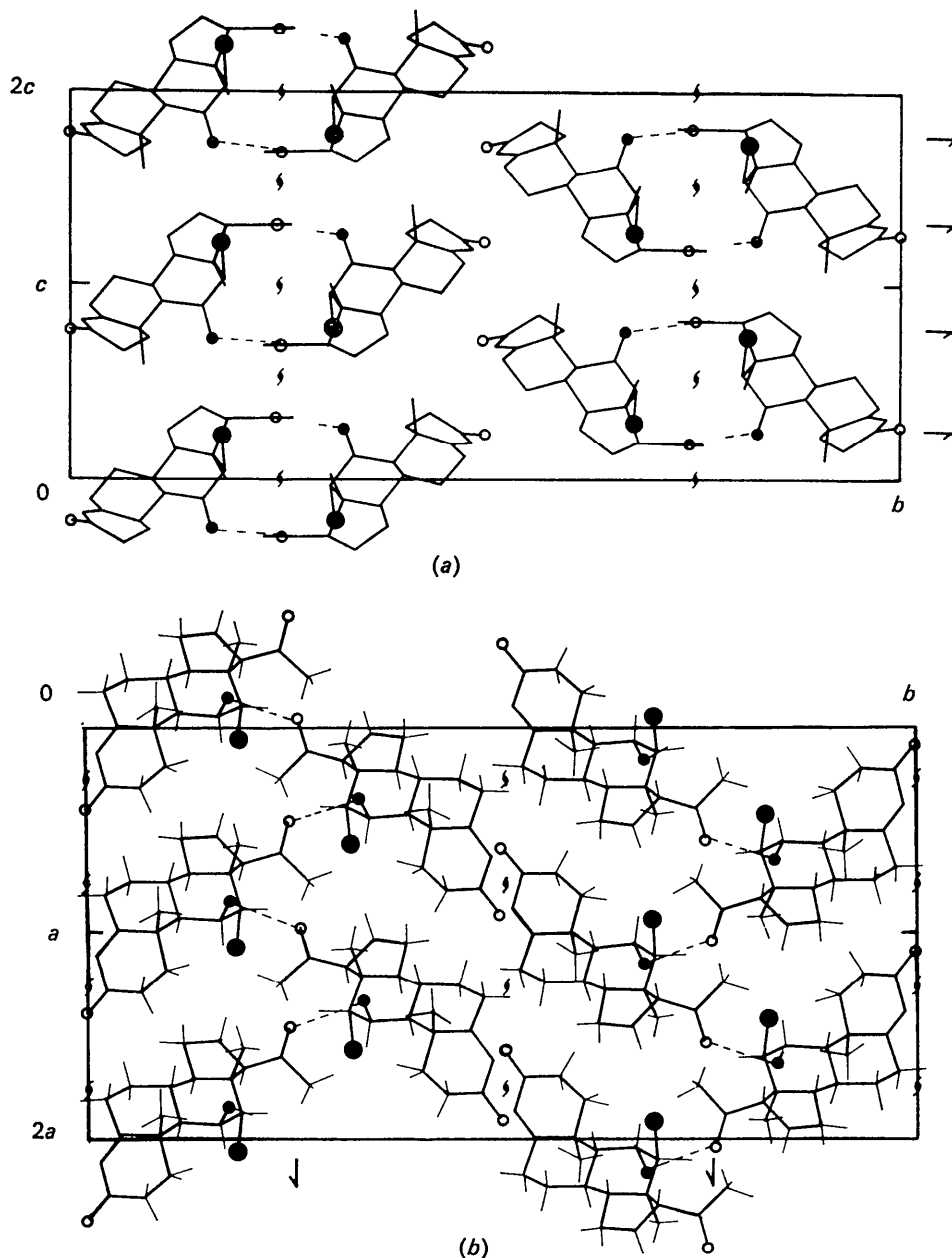


Fig. 10. Projections of four unit cells onto (a) the (100) plane and (b) the (001) plane. Ketone oxygen, open circles; hydroxyl oxygen, small solid circles; bromine, larger solid circles.

lies 0.33 Å out of the plane of the acetyl group which is hydrogen bonded to it, and the angle H(11')...O=C(20) is  $122 \pm 2^\circ$ , indicating that the hydroxyl bond is probably directed toward one of the lone pair orbitals of O(20).

The authors wish to express their gratitude to Mr C. T. Lu for his patient and meticulous collection of the intensity data used in this investigation. They also wish to thank Dr K. Johnson, who supplied his program *ORTEP*, with which several of the Figures in this paper were produced, and Mrs K. DeVine and Mr A. Greaver for their assistance in preparing these Figures.

This investigation was supported by Public Health Research grant number CA-06183 from the National Cancer Institute.

#### References

- ALLEN, H. C. & PLYLER, E. K. (1958). *J. Amer. Chem. Soc.* **80**, 2673.  
 ASHIDA, T., HIROKAWA, S. & OKAYA, Y. (1965). *Acta Cryst.* **18**, 122.  
 BARTELL, L. S. (1959). *J. Amer. Chem. Soc.* **81**, 3497.  
 BARTELL, L. S. & BONHAM, R. A. J. (1960). *J. Chem. Phys.* **32**, 824.  
 BUSING, W. & LEVY, H. A. (1964). *Acta Cryst.* **17**, 142.  
 COOPER, A., GOPALAKRISHNA, E. M. & NORTON, D. A. (1968). *Acta Cryst.* In the press.  
 CRUICKSHANK, D. W. J. (1956*a*). *Acta Cryst.* **9**, 747.  
 CRUICKSHANK, D. W. J. (1956*b*). *Acta Cryst.* **9**, 754.  
 CRUICKSHANK, D. W. J. (1961). *Acta Cryst.* **14**, 896.  
 FRIED, J. (1957). *Cancer*, **10**, 752.  
 FRIED, J. & SABO, E. F. (1953). *J. Amer. Chem. Soc.* **75**, 2273.  
 HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502.  
 HENDRICKSON, J. B. (1961). *J. Amer. Chem. Soc.* **83**, 4537.  
 HERZ, J. E., FRIED, J. & SABO, E. F. (1956). *J. Amer. Chem. Soc.* **78**, 2017.  
*International Tables for X-ray Crystallography* (1962). Vol. III. Birmingham: Kynoch Press.  
 JENSEN, L. H. (1962). *Acta Cryst.* **15**, 433.  
 KLYNE, W. & PRELOG, V. (1960). *Experientia*, **16**, 521.  
 LONSDALE, K. & MILLEDGE, J. (1961). *Acta Cryst.* **14**, 59.  
 NORTON, D. A. (1965). *Biophys. J.* **5**, 425.  
 REICHSTEIN, T. & FUCHS, H. G. (1940). *Helv. Chim. Acta.* **23**, 684.  
 ROBINSON, M. J. T. & WHALLEY, W. B. (1963). *Tetrahedron*, **19**, 2123.  
 SUTTON, L. E. (1965). *Tables of Interatomic Distances and Configuration in Molecules and Ions*. Spec. Publ. No. 18. London: The Chemical Society.  
 TRUEBLOOD, K. N. & SCHOMAKER, V. (1968). *Acta Cryst.* **B24**, 63.  
 WALLWORK, S. C. (1962). *Acta Cryst.* **15**, 758.  
 WILSON, A. J. C. (1942). *Nature, Lond.* **150**, 151.

*Acta Cryst.* (1968). **B24**, 824

## The Crystal and Molecular Structure of 3 $\beta$ ,17 $\alpha$ -Dihydroxy-21-bromo-5 $\alpha$ -pregnan-11,20-dione\*

BY JEAN M. OHRT, A. COOPER,† GOPINATH KARTHA AND DORITA A. NORTON†

*Center for Crystallographic Research, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.*

(Received 21 August 1967)

The crystal structure of 3 $\beta$ ,17 $\alpha$ -dihydroxy-21-bromo-5 $\alpha$ -pregnan-11,20-dione has been determined by three-dimensional X-ray analysis and refined to a final *R* value of 0.096. Unit cell constants are  $a = 12.039$ ,  $b = 10.875$ ,  $c = 7.605$  Å,  $\beta = 97.55^\circ$ , space group *P*2<sub>1</sub>. Standard deviations for bond lengths and angles are in the ranges of 0.01–0.02 Å and 0.8–1.3°, respectively. Molecules related by unit-cell translations in the *a* direction are hydrogen bonded *via* the 3 $\beta$ -hydroxyl oxygen atom and the 17 $\alpha$ -hydroxyl hydrogen atom. The 3 $\beta$ -hydroxyl hydrogen atoms hydrogen-bond to the 11-ketone oxygen atoms of molecules related by the screw axes.

#### Introduction

As a continuation of the studies on molecular stacking determinants and structural-functional relationships of

steroids, as described in our earlier papers (Norton, 1965; Norton & Ohrt, 1966), the crystal structure of 3 $\beta$ ,17 $\alpha$ -dihydroxy-21-bromo-5 $\alpha$ -pregnan-11,20-dione (Fig. 1) has been determined by X-ray analysis. The non-halogenated steroid, 3 $\beta$ ,17 $\alpha$ ,21-trihydroxy-5 $\alpha$ -pregnan-11,20-dione (Reichstein's substance D), is an intermediate metabolite in the enzymatic degradation of cortisone and has been isolated from the adrenal cortex and liver (Dorfman & Ungar, 1954; Fieser & Fieser, 1959).

\* This investigation was supported in part by the following grants: U.S.P.H. Research Grant CA-06183 and U.S.P.H. Career Development Award GM-K3-16737 from the National Institutes of Health.

† Present address: The Medical foundation of Buffalo, 73 High Street, Buffalo, New York 14203, U.S.A.